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Lancaster General Hospital

Pages are perforated for easy removal. →
Fold twice in each direction before tearing.

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FROM THE EDITOR'S DESK

Carbon Monoxide Poisoning

Keeping Our Patients Safe

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Editor in Chief

Carbon Monoxide Awareness Month is just behind us, recognized each November as cold weather begins to blanket the United States. That makes this issue of *JLGH* a good place to talk about carbon monoxide (CO), since our winter heating needs bring increased risk of CO poisoning. Let's begin by revisiting our pathophysiology regarding hemoglobin and oxygen transport.

Carbon monoxide (CO) is a product of burning any fossil fuel, and hemoglobin has an affinity for CO that is 200 times greater than its affinity for oxygen; myoglobin binds CO even more readily. Carboxyhemoglobin impairs the ability of the cells to burn oxygen and decreases ATP synthesis; this leads to short-term sequelae such as dyspnea, headache, weakness, and nausea.

Long-term exposure can yield lipid peroxidation, as well as white matter and cardiac changes, increasing the risk for neurologic and cardiac pathology. While our most vulnerable patients — infants, the elderly, and those with chronic illness — are most at risk, any of us can be affected when concentrations are high enough.

As many as 95,000 people per year in the United States are sickened by CO exposure, leading to 50,000 hospitalizations and between 1,000 and 1,500 deaths, according to independent registries.[1] The age-adjusted CO-related deaths per 100,000 people for 2020 (the most recent year data are available) is 47 in the state of Pennsylvania.[2] Undoubtedly, thousands are made sick each year by this odorless gas, and as alluded to above, we are most at risk during the winter months, when we are less likely to ventilate our homes and more likely to use indoor heating sources.

For example, CO poisoning can occur during power outages when people rely on portable generators, which can create up to 100 times the carbon monoxide of an efficient fuel-burning car. Portable generators should be kept at least 25 feet from the house and away from vents, doors, and open windows.

Warming the car in the garage is also common but is not without risk, even when the garage door is open. Leaving garage doors open is insufficient to appropriately ventilate, since CO particles can penetrate dry wall.[2] Large engines or several small engines burning in poorly ventilated areas can quickly create a dangerous situation. Recreation vehicles, public garages, and even the trailers that maintenance workers use to haul service vehicles to and from job sites are setups for chronic higher-than-appropriate exposure. In truth, there is no normal exposure level.

Unfortunately, misdiagnosis of CO poisoning is common, with as many as 30% of cases being attributed to food poisoning. While carboxyhemoglobin can be tested using venous blood, results often take time, and levels vary in smokers versus nonsmokers. Use of multiwave fingertip meters can help, although many clinicians would await confirmation with venous values.

Treatment in the acute stage begins with removing a patient and any others from the exposure. High-dose oxygen, for example by non-rebreather for between four and five hours, will improve acute symptoms. Hyperbaric therapy is recommended for patients who are most vulnerable, including patients who are pregnant or have chronic respiratory conditions.

While there is no access to acute hyperbaric therapy in Lancaster, we have the capacity to transport patients for hyperbaric oxygen if necessary, and there is 24-hour capacity at Penn Medicine's multiplace hyperbaric chamber, which can seat several patients at one time. While this offering is a blessing for many of our patients, thinking back to Carbon Monoxide Awareness Month reminds us of the importance of prevention.

So, what can we as leaders in our community do? We can coach patients about hazards and how to prevent risks. We can remind patients to keep chimneys and vents clean, to get leaks in exhaust systems repaired, and to never use engines indoors. They should carefully monitor heating elements, and we should *all* be mindful about ventilation around any fuel-burning engine.

CO monitors, which became widely available in the 1990s and now cost $35 to $60, should be installed on every floor of a dwelling and especially close to where people sleep. Smoke detectors are not the same as CO detectors, and while combination detectors are available, lack of mandates on maintaining CO detectors

*A version of this editorial previously appeared in LNP, *Lancaster County's daily newspaper.*

and higher costs of combination detectors are deterrents. Unfortunately, only 14% of U.S. homes currently have functioning monitors.[1]

As public health denizens, we can advocate for more ubiquitous detector use and support agencies that help fund detectors for low-income housing, hotels, and businesses. A white paper is currently being circulated by the National Carbon Monoxide Awareness Association advocating for the lowering of detection limits on commercial detectors. Again, there is no "normal" amount of CO to which we should be exposed, and it remains unclear at this time what long-term exposure may do to the health of our citizens. Detector batteries should be changed frequently, and detectors replaced every 5 to 10 years.

Should detectors be placed in child care facilities? State House Bill 494 and State Senate Bill 129[3] would support such a move. And why not go even further? Why not consider detectors in vehicles? In parking garages? In sheds and hangars? Product information at the point of sale may also be helpful. Any generator or small engine can create carbon monoxide, and notices to consider detector purchase may help save lives.

Carbon Monoxide Awareness Month restarts the conversation every year about how we can help protect our patients from CO hazards. Won't you join me in extending the conversation to our patients?

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JLGH Fall 2023 Recap

Q&A for Extended Learning

The Fall issue of The Journal of Lancaster General Hospital *offered updates in the treatment of sexually transmitted diseases and clinician burnout, as well as a photo quiz about impetigo. Review the questions and answers below to see how much you remember from the issue. Need a refresher? All issues of* JLGH *are available online at JLGH.org.*

Q **How often does the Centers for Disease Control and Prevention (CDC) recommend HIV screening for asymptomatic patients ages 13-64 years?**

A At least once in their lifetime.

Q **Clinicians can consider testing women with pelvic inflammatory disease for *M. genitalium*. How can this be ordered at LG Health?**

A Providers should order an "unidentified lab" and specify "*Mycoplasma genitalium* PCR," which can be performed on an endocervical, vaginal, urethral, or urine specimen.

Q **Bullous impetigo should probably be treated with oral antibiotics. What can be added to the bath water to help treat recurrent cases of impetigo? How long after beginning antibiotics should patients be considered contagious?**

A 1. Less than a capful of bleach in a tub full of water.
2. 24-48 hours.

Q **In an article about stress and burnout in health care workers, what strategies were offered for employers to help workers stay engaged in their service to patients?**

A Health care leaders may implement mitigation strategies including: setting clear and well-defined boundaries; requiring scheduled breaks; finding ways to reduce the workload; and facilitating various destressing techniques, such as deep breathing, mindfulness, and time management.

Q **In "The X-Waiver and the Culture of Addiction Medicine," Dr. Jon Lepley notes that what percentage of individuals who could receive medical treatment for opioid use disorder actually do?**

a. 5% b. 15% c. 25% d. 55%

A The answer is:
b. 15%. We hope that the elimination of the need for the X-waiver will result in better access to lifesaving treatment.

A Case of Myocardial Infarction with No Obstructive Coronary Atherosclerosis

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CLINICAL PRESENTATION

A 56-year-old male with a past medical history of hypertension, hyperlipidemia, and benign prostatic hyperplasia presents to the emergency department (ED) for severe mid-sternal chest pain with exertion, without associated dyspnea. He describes a pressure/burning-like sensation that radiates to the left arm and is associated with a numbness/tingling sensation. He notes similar episodes for the previous two weeks, but pain has subsequently become worse. The patient has taken three to four ibuprofen pills daily but denies acid reflux symptoms. He also has been under a great deal of stress as a caregiver for a family member.

In the ED, the chest discomfort decreases to 3/10 after receiving three sublingual nitroglycerin tablets and intravenous morphine. The pain is reproducible and worsens with movement of his arm; he has musculoskeletal arthralgias but no other complaints on a review of systems.

His past medical history includes benign prostatic hypertrophy, hypercholesterolemia, and hypertension. He had a normal cardiac catheterization in 2008. The patient's family history includes diabetes and hypertension but not heart disease, and he has never smoked and says that he only drinks small amounts on social occasions.

His medications include albuterol inhaler as needed, atorvastatin 20 mg daily, ibuprofen 600 mg as needed, lisinopril 10 mg daily, tamsulosin 0.4 mg twice daily, and triamterene-hydrochlorothiazide (Dyazide®) 37.5 mg/25 mg daily.

On physical examination, he is afebrile with normal vital signs. He appears uncomfortable, moaning and groaning, with no other focal findings. Labs reveal an elevated fifth-generation troponin test of 121.80 ng/L; repeated two hours later, that number rises to 154 ng/L. The comprehensive metabolic panel and complete blood count are unremarkable, and an electrocardiogram is normal.

Computed tomography (CT) scan of the head without contrast reveals no intracranial hemorrhage, mass effect, or midline shift. A chest X-ray series demonstrates a normal cardiomediastinal silhouette, clear lungs, and bones that appear grossly unremarkable; however, there is mild hilar lymphadenopathy. CT angiogram of the chest reveals no evidence of pulmonary embolism, but again there is hilar and mediastinal lymphadenopathy.

The working diagnosis is non-ST-elevation myocardial infarction, thus a cardiology consult is obtained to consider cardiac catheterization. In the meantime, an echocardiogram is essentially normal with a left ventricular ejection fraction of 55% to 60% with normal diastolic function, and there is no evidence of left ventricular regional wall motion abnormality and no significant valvular pathology.

Cardiac catheterization reveals mild coronary artery disease with a 20% ostial left circumflex artery stenosis. There is no evidence of a recanalized lesion, distal cutoff, or spontaneous coronary artery dissection. Since the echocardiogram did not reveal any regional wall motion abnormalities, the acute myocardial injury is felt to be of unclear mechanism.

A cardiac MRI is performed and reveals normal biventricular function with no segmental wall motion abnormalities, with normal left and right ventricular ejection fractions. There is focal myocardial delayed enhancement at the basal inferolateral wall extending from the mid-myocardium to epicardial region (see Fig. 1 on page 100). This is suspicious for cardiac

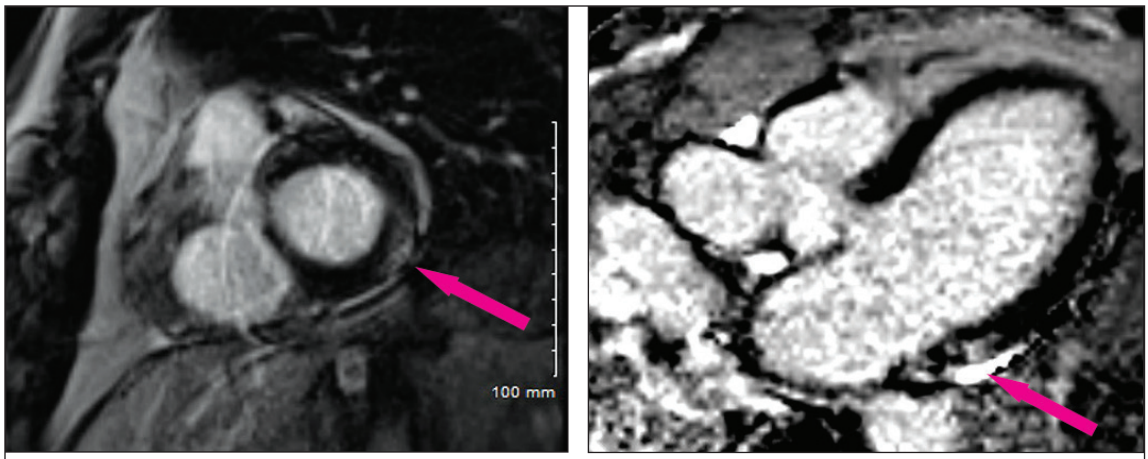


Fig. 1. Cardiac MRI images demonstrating a subepicardial inferolateral delayed enhancement pattern in short-axis imaging (left) and three-chamber long-axis imaging (right).

sarcoidosis (CS), particularly given the abnormal findings on the chest radiography.

Prior myocarditis could also be included in the differential diagnosis. There is no evidence of edema on short tau inversion recovery (STIR) imaging, a finding that may have suggested acute myocarditis. No significant valvular dysfunction is noted; trace pericardial effusion is reported, yet no abnormal pericardial thickening or enhancement is found.

DISCUSSION

The initial diagnosis was non-ST-elevation myocardial infarction. This was modified after cardiac catheterization to myocardial infarction with no obstructive coronary atherosclerosis (MINOCA) versus non-ST-elevation myocardial infarction type 2 (NSTEMI type 2).[1] MINOCA is a clinical syndrome defined by evidence of a myocardial infarction with no significant coronary artery disease (<50% stenosis severity).

The Fourth Universal Definition of Myocardial Infarction, published by the European Society of Cardiology in 2018, added MINOCA as a subset of myocardial infarction, requiring three criteria for diagnosis[2,3]:

1. The diagnosis of myocardial infarction must be established.
2. Coronary arteriography should reveal non-obstructive (<50% stenosis) coronary arteries.
3. No other diagnosis, such as pulmonary embolism or renal failure, can explain the clinical presentation.

Patients with MINOCA are more likely to be female and younger, in comparison with NSTEMI type 1.[4] MINOCA represents 6% (range 1% to 14%) of all myocardial infarctions and can be subcategorized into coronary, cardiac, and non-cardiac causes (see Table 1). In a meta-analysis, in-hospital mortality of MINOCA is 0.9%, and one-year mortality is 4.7%.[5,6]

Table 1. **Differential Diagnosis of MINOCA**[7]

Coronary	
Coronary artery spasm	
Transient coronary artery thrombosis with autolysis	
Coronary artery dissection	
Coronary artery embolism	
Cardiac	
Takotsubo cardiomyopathy	Tachycardia
Microvascular dysfunction	Cardiac sarcoidosis
Viral myocarditis	
Non-Cardiac	
Pulmonary embolism	Shock
Aortic dissection	Hypoxia
Renal impairment	Other cardiomyopathies

DIAGNOSTIC TECHNIQUE

Cardiac MRI is helpful in elucidating the etiology of MINOCA. It is the preferred next test after both echocardiography and cardiac catheterization do not reveal a clear etiology of the myocardial infarction.[8] Early use of cardiac MRI enables identification of potentially reversible causes and assists in treatment/prognosis. Failure to identify causes can lead to undertreatment.

Late gadolinium enhancement (LGE) on cardiac MRI is believed to reflect myocardial fibrosis. Additional imaging techniques, such as T1 mapping, extracellular volume (ECV), T2 mapping, and STIR

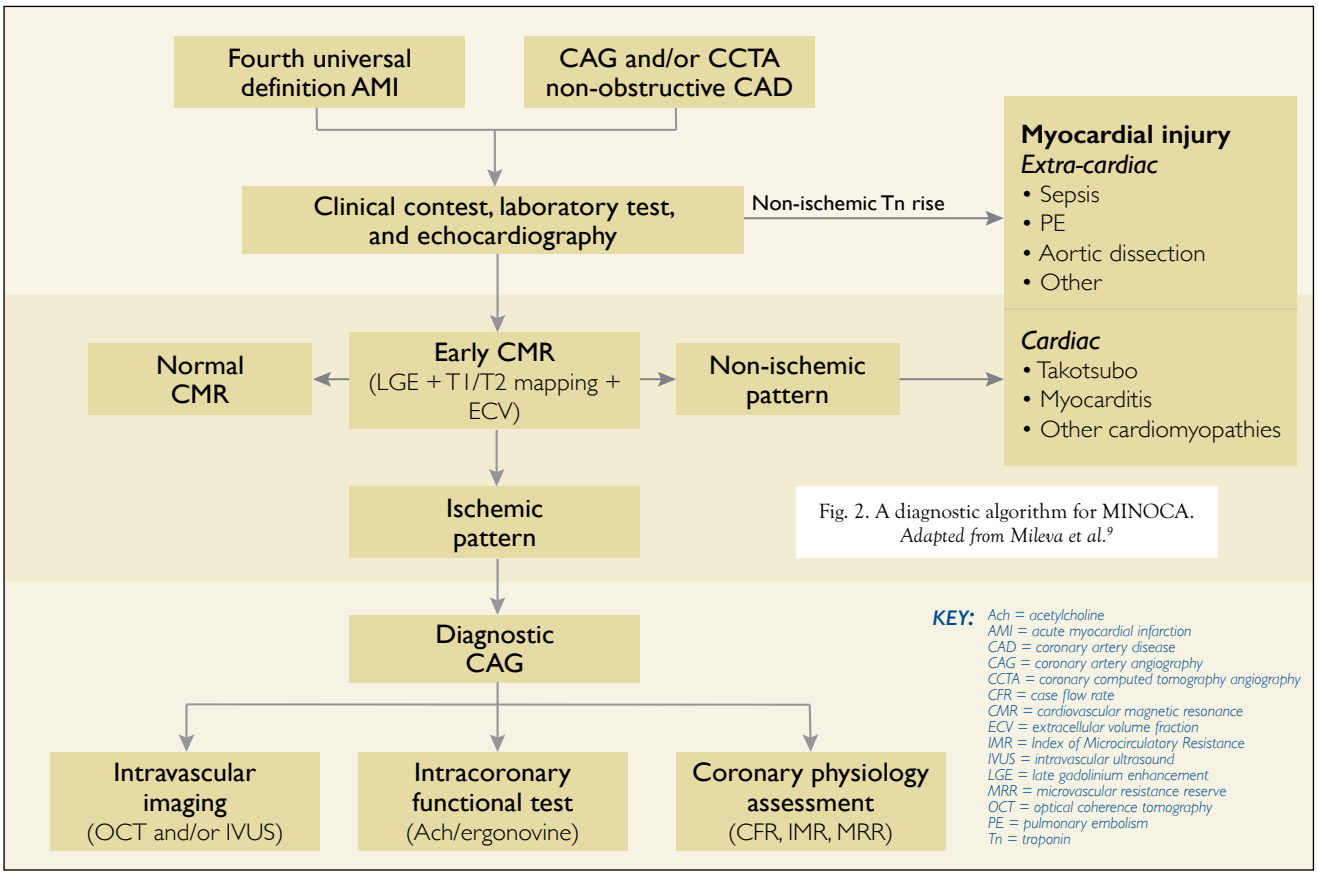


Fig. 2. A diagnostic algorithm for MINOCA. *Adapted from Mileva et al.*[9]

weighted imaging, can reveal evidence of acute myocarditis. Varying patterns of LGE correlate with and suggest specific cardiac pathologies without necessitating myocardial biopsy for tissue characterization. These include infarction, myocarditis, and cardiomyopathies.

Quantification of the extent of myocardial LGE helps stratify the prognosis. Approximately 25% of patients with MINOCA are found to have a normal myocardium after cardiac MRI, and a clear etiology of the presentation is not elucidated. Cardiac MRI reclassifies 68% of patients with MINOCA and confirms myocardial infarction in 22%, providing valuable diagnostic and prognostic information (see Fig. 2).[9] Transesophageal echocardiography can be considered in cases of suspected coronary artery embolism.

TREATMENT OF MINOCA

Dual antiplatelet therapy with aspirin and $P2Y_{12}$ inhibition have not been found to improve outcomes in MINOCA. Statin and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use resulted in a 23% and 18% reduction in major adverse cardiovascular outcomes, respectively, in the SWEDEHEART registry consisting of more than 9,000 MINOCA patients.[10] Beta-blocker therapy may have provided some benefit to patients in this registry, but there have been no major randomized clinical trials of this treatment for patients with MINOCA.

In our patient, a CT angiogram of the chest revealed mediastinal and hilar lymphadenopathy with no evidence of pulmonary embolism, and the cardiac MRI demonstrated subepicardial delayed gadolinium enhancement of the inferolateral wall, consistent with cardiac sarcoidosis. Therefore, CS was the working diagnosis.

The patient did not demonstrate ventricular arrhythmias and did not undergo an electrophysiology study. Instead, he was discharged from the hospital with a plan for outpatient telemetry monitoring and positron emission tomography (PET) scan. The latter was unremarkable, suggesting burnt-out CS without active inflammation. Immunosuppressive therapy for CS was not initiated.

CS PREVALENCE AND TREATMENT OPTIONS

Sarcoidosis is a heterogeneous multisystem disease of unknown etiology, characterized by the formation of noncaseating granulomas.[11] The etiology of CS is

unknown. Approximately 5% of patients with sarcoidosis have cardiac involvement, making CS a rare condition. Up to 25% of CS cases are isolated without involvement of extracardiac tissues.[12,13]

Countries in more northern latitudes may have higher prevalence of cardiac sarcoidosis, like sarcoidosis in general, yet registries are incomplete.[14] It can present asymptomatically, although patients may have ventricular arrhythmia or high-grade block, may experience palpitations or syncope, and may even present with congestive heart failure (CHF) or with sudden cardiac death. Atrial arrhythmias are uncommonly associated with CS.

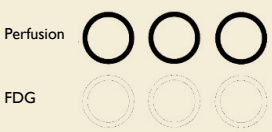
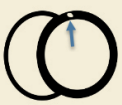
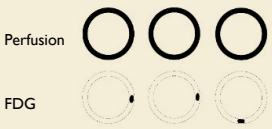
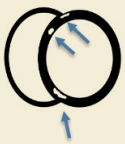
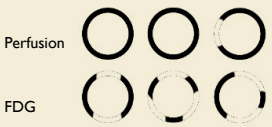
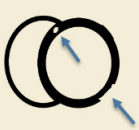
Approximately 14% of CS patients initially present with sudden death. Sudden death due to ventricular tachyarrhythmias or conduction block accounts for 25% to 65% of CS-associated mortality. CHF accounts for 20% of initial presentations. Elevated levels of cardiac troponins, serum angiotensin converting enzyme (ACE), and urinary calcium have been reported in CS.

Computed tomography, cardiac MRI, and cardiac PET scans are utilized in the diagnosis,[15-18] which can be very difficult to establish.[19] Imaging techniques, diagnostic criteria for extra-cardiac disease, and endomyocardial biopsy are utilized to confirm the diagnosis. Cardiac MRI and PET scanning (see Table 2) are often used as diagnostic gold standards for CS.[20-23] Varying patterns of myocardial delayed enhancement on cardiac MRI and fluorodeoxyglucose (FDG) uptake on PET scanning correlate with an increased likelihood of CS.[24]

Endomyocardial biopsy is generally reserved for cases of high clinical suspicion with non-diagnostic imaging.[25,26] Given the sparse location of myocardial granulomas, random septal biopsy may result in a high rate of falsely negative specimens.

Histological confirmation of noncaseating granuloma on extracardiac biopsy can help confirm the diagnosis in the right clinical setting. Therefore, cardiac MRI may play a greater role in risk stratification of patients with systemic or suspected cardiac sarcoidosis. Further, biventricular LGE is associated with markedly increased odds of ventricular arrhythmias (OR = 43.6; 95% CI: 16.2-117.2), and the absence of delayed en-

Table 2. **Patterns of Cardiac MRI and PET Imaging in the Diagnosis of Cardiac Sarcoidosis**
Adapted from Vita et al.[23]

Likelihood Probability	MRI Likelihood	MRI Example	PET Likelihood	PET Example
No CS (<10%)	No late gadolinium enhancement (LGE).		No perfusion defect **and** no F-fluorodeoxyglucose (FDG) uptake.	
Possible CS (10%-50%)	One focal area of LGE.		No perfusion defect and nonspecific FDG uptake.	
Probable CS (50%-90%)	Multifocal LGE in a pattern consistent with CS, but cannot rule out myocarditis.		Multiple focal areas of FDG uptake +/- small perfusion defects.	
Highly Probable CS (>90%)	Multifocal LGE in a pattern strongly consistent with CS.		Multiple focal areas of FDG uptake or multiple perfusion defects.	

hancement is associated with a very low risk of adverse cardiac events and likely excludes the presence of cardiac sarcoidosis.

Treatment options for CS can include immunosuppressants to improve ejection fraction and decrease ventricular arrhythmias associated with active inflammation[24,27,28] (see Fig. 3). Prednisone in doses of 60 mg to 80 mg/day have been suggested and may be tapered if effective to a maintenance dose of 10 mg to 15 mg/day. In those patients for whom this is not effective, anti-malarial drugs, methotrexate, or azathioprine should be considered.[29]

High-grade atrioventricular block necessitates pacemaker implantation. However, when ventricular arrhythmias cannot be

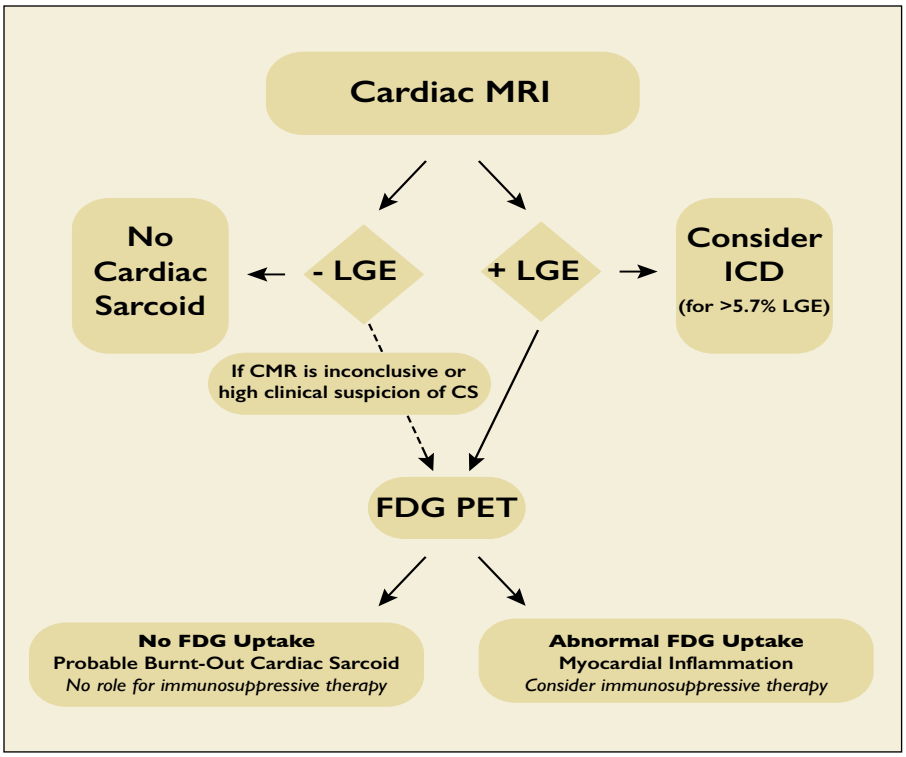


Fig. 3. A suggested algorithm for the diagnosis and immunosuppressive treatment of cardiac sarcoidosis.
Adapted from Vita et al.[23]

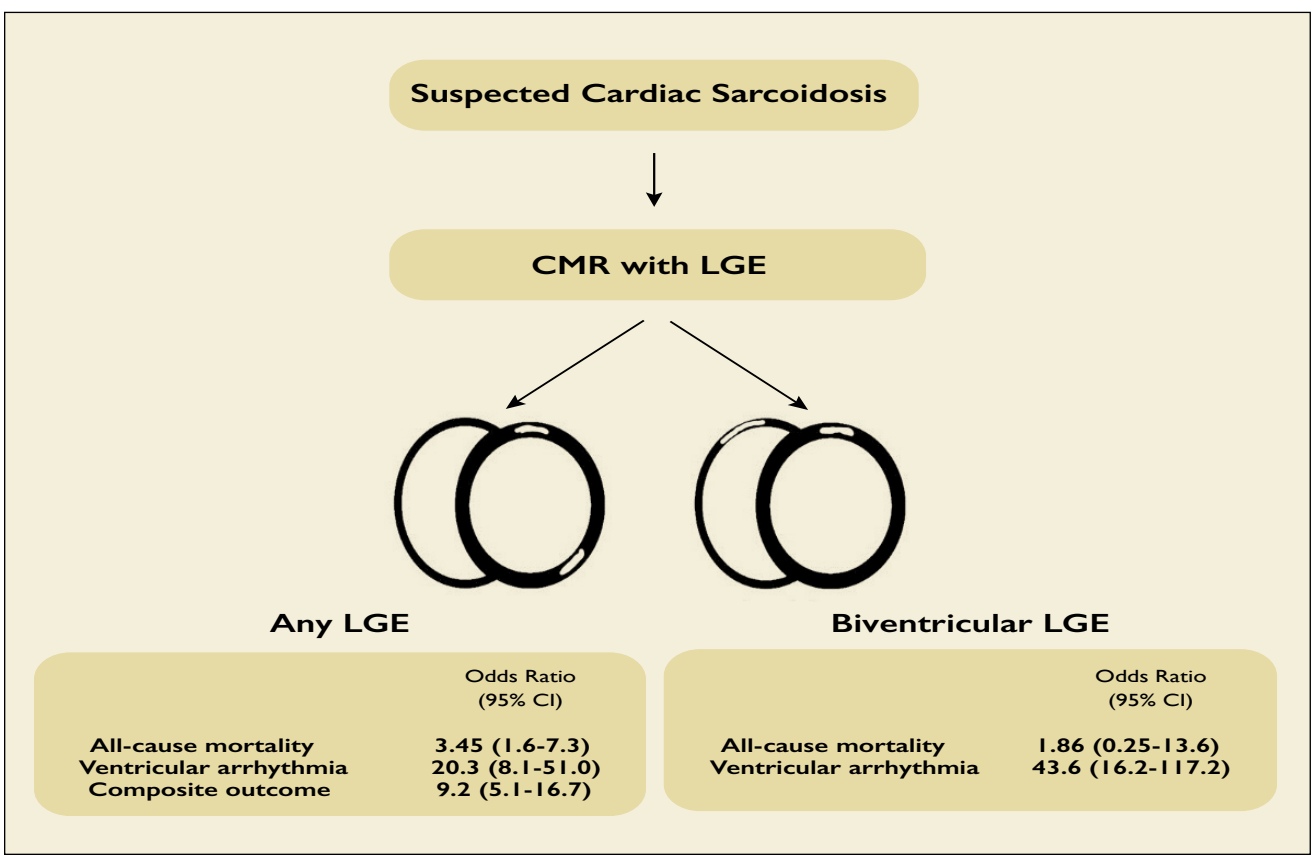


Fig. 4. Prognostic significance of late gadolinium enhancement (LGE) with known or suspected cardiac sarcoidosis.
Adapted from Stevenson et al.[28]

controlled, antiarrhythmic therapy, catheter ablation, and cardioverter defibrillator implantation may be necessary. Recent data suggest that the presence and quantity of abnormal delayed enhancement during cardiac MRI correlates significantly with an increased risk of ventricular arrhythmias and mortality (see Fig. 4 on page 103).[28] Refractory ventricular arrhythmias and heart failure may necessitate advanced heart failure therapies, such as biventricular assist device or cardiac transplantation.

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Lepley

CASE VIGNETTE

A 38-year-old man presents to his primary care provider to establish care. He is obese and mildly hypertensive, with a BMI of 32 and blood pressure measuring 142/86. He does not smoke cigarettes or use illicit drugs but reports consuming a six-pack of beer four days per week. Sometimes he drinks even more heavily, leading to arguments with his spouse and a hangover the next day.

He occasionally misses work after a very heavy drinking day. He has tried to quit drinking but usually only manages to abstain for a few weeks before returning to his previous pattern. He has not consumed alcohol for the past five days but reports routinely feeling the urge to purchase alcohol on his way home from work. He does not display any symptoms of clinical depression. He is not interested in behavioral counseling but is willing to consider medication to help him cut back on his alcohol use.

BACKGROUND

Excess alcohol consumption is associated with short-term and long-term health consequences. The impairing effects of alcohol predispose individuals to being involved in motor vehicle accidents, perpetrate intimate partner violence, and undertake risky sexual behaviors that can result in unintended pregnancy or sexually transmitted diseases. Over time, heavy consumption of alcohol is associated with many chronic health problems, including obesity, hypertension, sleep apnea, and gastrointestinal cancers.[1]

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines heavy alcohol consumption as more than four drinks per day or more than 14 drinks per week for men, and more than three drinks per day or more than seven drinks per week for women.[2] The rationale for these differences is based on variation in biological factors between sexes, and these recommendations are based on sex assigned at birth rather than gender identity.

Although excess alcohol consumption is associated with health risks, alcohol use disorder (AUD) is not defined by how much alcohol is consumed. The essential features of AUD are a compulsion to drink alcohol, impaired control over alcohol use, and negative consequences that result from alcohol consumption. A diagnosis of AUD is made by clinical interview. Diagnostic criteria are defined in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (see Table 1 on page 106).[3]

Naltrexone is one of three medications approved by the Food and Drug Administration (FDA) to treat AUD. The other two medications are acamprosate and disulfiram. The recommended dosing of acamprosate involves taking six capsules daily; its utility is limited by difficulty adhering to this regimen. Disulfiram causes a severe aversive reaction in the face of alcohol consumption, and these adverse effects, poor adherence, and lack of published effectiveness limit its use.[4] As a result, naltrexone is generally considered the mainstay of treatment.

PATHOPHYSIOLOGY

Alcohol exerts an influence on four critical neurotransmitter systems in the brain. These are gamma-aminobutyric acid (GABA), glutamate, dopamine, and endogenous opioids (endorphins). GABA is an inhibitory neurotransmitter that suppresses neuronal excitability throughout the central nervous system. Glutamate is the most abundant excitatory neurotransmitter in the brain and plays a crucial role in shaping learning and memory.[5] Dopamine and endorphins exert influence within the ventral tegmental area (VTA) and nucleus accumbens (NAc) — brain regions involved in reward, pleasure, and assignment of salience to environmental cues.

Alcohol's influence over these neurotransmitters is dose dependent. Relatively low doses of alcohol can stimulate glutamate, dopamine, and endogenous opioid activity in the VTA and NAc. This may produce a sensation of arousal and increased energy.[6] These effects may be responsible for the reinforcement of alcohol use despite negative consequences in people who develop an AUD. Naltrexone exerts blockade at opioid receptors within the VTA and NAc (see Fig. 1) to reduce or eliminate the reinforcing effects of alcohol.[7]

At higher doses, alcohol mimics the effects of GABA and suppresses the excitatory neurotransmitter glutamate.[8] The effect on GABA accounts for alcohol's potential to cause somnolence and impaired motor function during intoxication. Abrupt cessation of alcohol after prolonged heavy consumption is associated with a surge in glutamate activity causing neurologic excitation associated with an alcohol withdrawal syndrome.[9] Naltrexone attenuates the opioid-mediated release of GABA in the VTA (see Fig. 1) but does not offset the impairing effects of alcohol or prevent or treat alcohol withdrawal.

Functional neuroimaging studies demonstrate differential effects in these neurochemical pathways among people with AUD compared to social drinkers.[10,11] Individuals with AUD will crave alcohol during periods of abstinence due to increased recruitment of stress peptides in the extended amygdala and experience a powerful reinforcing effect through dopaminergic pathways in the NAc.[12] This contributes to an inability to control their use, heavy consumption, and development of tolerance. The pattern of alcohol use that emerges results in short-term impairment, long-term physical health problems, and adverse psychosocial consequences. These observable features that define AUD are rooted in neurobiology gone awry and validate the conceptualization of AUD as a brain disease.

SCOPE OF THE PROBLEM

In a 2021 national survey, 29.5 million people in the United States over 12 years of age had AUD in the past year.[13] This equates to 10.6% of the adult and adolescent population. Alcohol is the most common substance implicated in substance use disorders, with affected individuals outnumbering those affected by marijuana, cocaine, heroin, hallucinogenic agents, inhalants, methamphetamine, and prescription drugs combined.[13] People aged 18 to 25 years are most likely to have an AUD, encompassing 15% of people in this demographic.

The environmental factors associated with the COVID-19 pandemic have contributed to a remarkable surge in the prevalence of AUD. Over the first two decades of the 21st century, the United States saw a gradual decline in the prevalence of AUD from 7.7% in 2002 to 5.3% in 2019.[14] The alarming spike in 2021 to more than 10% of the population with AUD

Table 1. Alcohol Use Disorder Diagnostic Criteria[3]

1	Alcohol is often taken in larger amounts or over a longer period than was intended.
2	There is a persistent desire or are unsuccessful efforts to cut down or control alcohol use.
3	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4	Craving, or a strong desire or urge to use alcohol.
5	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8	Recurrent alcohol use in situations in which it is physically hazardous.
9	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10	Tolerance, as defined by either of the following: a) a need for markedly increased amounts of alcohol to achieve intoxication or desired effect; b) a markedly diminished effect with continued use of the same amount of alcohol.
11	Withdrawal, as manifested by either of the following: a) the characteristic withdrawal syndrome for alcohol; b) alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

— Mild: The presence of 2-3 symptoms. — Moderate: The presence of 4-5 symptoms. — Severe: The presence of 6 or more symptoms. —

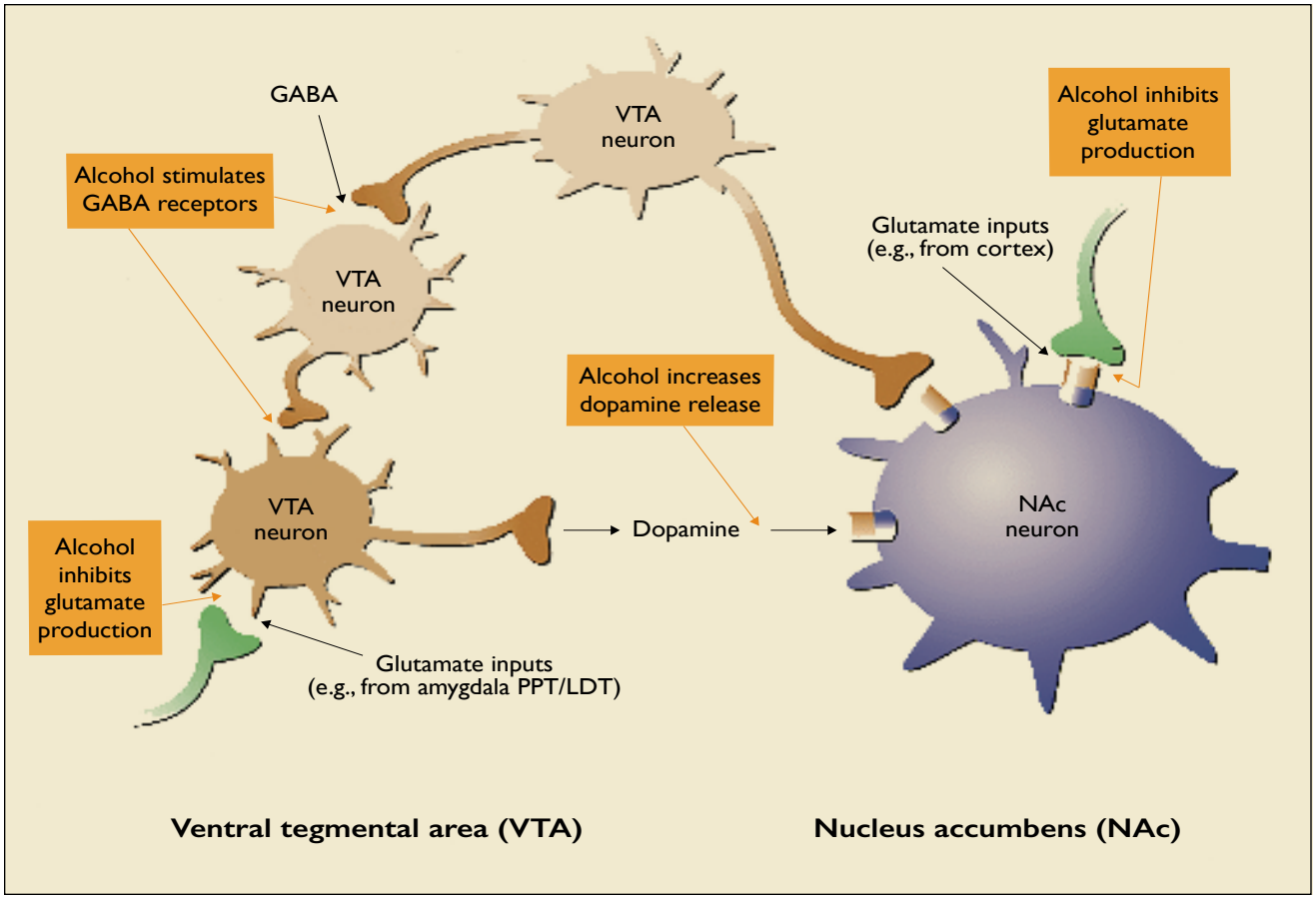

Fig. 1. Neurobiological pathways in alcohol use disorder.

may partly be explained by differences in data collection and a shift toward greater utilization of web-based surveys post-pandemic.[13] However, the COVID-19 pandemic and associated social isolation contributed to a secondary public health crisis around substance-related morbidity and mortality.

For the first time in 60 years, estimated life expectancy in the United States is in a state of decline.[15] Currently, alcohol contributes to nearly 15% of deaths among people aged 20 to 49 years and 20% of deaths that occur in people under 20 years of age.[16] Alcohol-related mortality increased by more than 20% in 2020 and 2021,[17] and alcohol has been implicated in 20% of substance overdose deaths in Lancaster County since the beginning of the COVID-19 pandemic.[18]

Despite this profound impact, AUD is often undiagnosed and inadequately treated. Fewer than 10% of people with AUD receive any treatment. Among the minority who receive treatment, effective medications are grossly underutilized, with just 1.6% of individuals with AUD reporting receipt of medication for their problem.[14]

EVIDENCE FOR EFFICACY OF NALTREXONE

Naltrexone is a semi-synthetic opioid with close structural similarity to oxymorphone, though it does not exert any agonist activity at the mu-opioid receptor. Instead, it is a competitive antagonist at mu-opioid receptors in the central nervous system. When treating AUD, this blockade may diminish dopaminergic effects that would otherwise reinforce alcohol consumption.[19] Additionally, naltrexone has been shown to reduce cravings for alcohol when alcohol-dependent individuals are exposed to environmental cues.[20]

Peak serum levels of naltrexone occur relatively quickly, about 60 minutes after oral administration, undergoing first-pass metabolism independent of cytochrome P450 enzymes, yielding its active metabolite 6-beta-naltrexol.[21] The elimination half-life of naltrexone and its active metabolite is 4 and 13 hours, respectively.[22]

Naltrexone was approved by the FDA to treat AUD in 1984 on the strength of animal models that demonstrated its efficacy.[23] Subsequent placebo-controlled trials showed that the medication reduces

alcohol cravings, supports alcohol abstinence, and reduces heavy drinking.[24,25]

While one multi-site trial involving 627 male Veterans Affairs patients characterized as "older, heavier drinkers, with long duration of alcoholism" failed to show evidence of long-term benefit from naltrexone 50 mg daily combined with psychosocial interventions,[26] the COMBINE study enrolled 1,383 patients among 11 academic sites and studied the effect of naltrexone 100 mg per day among individuals with less severe alcohol problems. In this trial, even without additional behavioral interventions, naltrexone reduced heavy drinking and improved rates of alcohol abstinence compared to placebo.[27] Systematic reviews further validate that naltrexone reduces heavy drinking and increases abstinence rates.[28,29]

Hepatotoxicity has historically been ascribed to naltrexone, but randomized controlled trials support that naltrexone is not hepatotoxic at therapeutic doses.[30,31] An expert panel convened by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2016 concluded that naltrexone treatment should not be delayed while awaiting results of liver function testing, and frequent testing in the absence of clinical findings such as jaundice, abdominal pain, nausea, or vomiting is unwarranted.[32] The safety and efficacy of naltrexone in individuals with a severe hepatic impairment such as cirrhosis are unknown, and caution in this population is warranted.

Concerns about medication adherence among people with AUD, paired with the relatively short half-life of naltrexone, have led to the development of a naltrexone 380 mg extended-release injectable formulation.[33] This is commonly known as naltrexone XR or its brand name Vivitrol®. Randomized controlled trials validate that naltrexone XR is superior to placebo in supporting a goal of abstinence and reducing heavy drinking.[33,34]

No prospective, double-blind, randomized controlled trials compare naltrexone XR to oral naltrexone when treating AUD. The superiority of one product over the other remains uncertain. The choice of naltrexone formulation can be individualized based on cost, patient preference, and ability to adhere to an oral formulation.

CLINICAL CONSIDERATIONS WHEN PRESCRIBING NALTREXONE

Naltrexone therapy is most effective when initiated after at least four days of abstinence from alcohol.[6,34] Individuals who consume alcohol daily for extended periods may develop alcohol withdrawal syndrome (AWS) when they attempt to abstain from alcohol. Untreated AWS can progress to seizures and delirium tremens, with a reported mortality rate of 1% to 5%.[35]

Clinicians should inquire about symptoms when their patient attempts to abstain from alcohol. Table 2 displays the Short Alcohol Withdrawal Scale,[36] which describes symptoms of AWS using lay terms. Patients who report these symptoms within 6 to 24 hours of abstinence from alcohol should receive medication treatment for AWS before beginning naltrexone treatment.

Ambulatory treatment of AWS by an experienced clinician may be considered for uncomplicated patients with mild-to-moderate symptoms.[37,38] Patients with a history of complicated withdrawal, seizures, delirium tremens, or co-occurring psychiatric disorders should be referred to a residential treatment setting for withdrawal management.[38] Patients using multiple substances also may be better served in a specialized residential treatment setting for substance withdrawal before naltrexone initiation.

Table 2. Short Alcohol Withdrawal Scale (SAWS)

Item	None (0)	Mild (1)	Moderate (2)	Severe (3)
Anxious				
Feeling confused				
Restless				
Miserable				
Problems with memory				
Tremors (shakes)				
Heart pounding				
Sleep disturbance				
Sweating				

The patients fill in the SAWS by ticking the appropriate boxes showing how they have been feeling for each of the 10 symptoms in the previous 24 hours. Each item is scored on a four-point scale: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. The scores are summed up to give a total score. Total scores suggest severity of withdrawal: mild withdrawal <12 points; moderate-to-severe withdrawal ≥12 points.

Adapted from Elholm et al.[36]

Naltrexone can precipitate withdrawal if administered to an individual with physiologic opioid dependence and can hinder the effectiveness of opioid analgesics. Therefore, naltrexone is contraindicated in patients who require long-term opioid therapy for chronic pain or opioid agonist treatment for opioid use disorder. Patients should abstain from all opioids for at least seven days before receiving naltrexone treatment. Patients who regularly used opioids before the period of abstinence should also undergo urine toxicology testing before starting naltrexone, as some opioids may linger and exert clinically significant effects beyond this seven-day window.[39]

Naltrexone should be initiated at 25 mg daily for the first week of treatment and then increased to 50 mg daily. Common adverse effects are nausea, vomiting, abdominal discomfort, headache, and fatigue; lower starting doses may minimize these effects.[6] Patients may continue taking naltrexone even if they return to drinking alcohol because naltrexone will not cause a disulfiram-like reaction in the face of alcohol consumption. Patients who continue to drink heavily despite adherence to naltrexone may increase their dose to 100 mg daily. Individuals who cannot adhere to a daily medication or do not display improvement with oral naltrexone may be candidates for monthly injections of naltrexone XR.

Because of the potential to hinder the effectiveness of opioids prescribed for pain, oral naltrexone should be discontinued at least three days before an elective surgery, and naltrexone XR should not be administered within six weeks of an elective surgery. Acute emergency pain management in a patient receiving naltrexone XR is a complex problem potentially requiring expertise from Pain Management and Anesthesiology. Patients receiving naltrexone XR should consider a medical alert card or bracelet to notify health care providers of their use of this medication in emergency or trauma settings.

Naltrexone may be more effective when combined with psychosocial interventions, though there is a consensus that no single counseling modality works best for every patient. Project MATCH was an ambitious NIAAA-sponsored study that sought to identify the best therapeutic modality for AUD based on individual patient characteristics.[40]

The study showed that cognitive behavioral therapy (CBT), motivation enhancement therapy (MET), and twelve-step facilitation (TSF) were equally effective at reducing alcohol consumption.[41] The only significant correlation revealed that patients with low psychiatric severity displayed more abstinent days with TSF compared to CBT,[41] and patients with high anger traits fared better with MET.[42]

A secondary analysis of Project MATCH data revealed low correlation between treatment attendance and effect size.[43] Many patients had good outcomes without receiving these interventions. Therefore, patients can be referred to adjunctive behavioral therapies, but medication should not be withheld when these interventions are declined or unavailable.

KEY TAKEAWAYS

Patients should abstain from all opioids for at least seven days before receiving naltrexone treatment.

Patients may continue taking naltrexone even if they return to drinking alcohol because naltrexone will not cause a disulfiram-like reaction in the face of alcohol consumption. Patients who continue to drink heavily despite adherence to naltrexone may increase their dose to 100 mg daily.

Patients should be advised to abstain from alcohol but to continue taking naltrexone and attend follow-up appointments if they fail to achieve that goal. Abstinence from alcohol is ideal, but a good clinical response may be defined by a substantial reduction in alcohol use to an amount that falls within limits defined by NIAAA.

Patients should be reassessed within one month of initiating treatment or changing the dose or formulation. Patients should be evaluated every three to six months after a good clinical response is achieved. The optimal duration of naltrexone treatment is unknown. Patients may consider medication discontinuation with close follow-up if they achieve a good clinical response over at least four months of treatment.[6]

CASE VIGNETTE CONCLUSION

The patient in the case vignette meets the criteria for a moderate AUD. He may find it reassuring to learn that this is a common medical problem with a basis in neurobiology and that effective treatments exist. He has abstained from alcohol for at least four days

without displaying a need for treatment of AWS. He does not use opioids or other illicit drugs, and there is no clinical suspicion of severe hepatic impairment. He is a good candidate for naltrexone treatment.

Naltrexone can be prescribed at a dose of 25 mg for the first six days and then increased to 50 mg daily. Clinicians should recommend baseline labs that include liver function testing, but medication should not be delayed or withheld pending these results. He should be reevaluated within one month of beginning the medication. If he fails to achieve a good clinical response, clinicians should inquire about medication adherence and consider increasing his dose to 100 mg daily or changing to naltrexone XR monthly injections.

After achieving a good clinical response, naltrexone should be continued for at least four months. The patient's need for treatment of hypertension and obesity should be reevaluated in the context of the elimination of unhealthy alcohol use as a contributing factor. If his relationship problems and absenteeism at work do not resolve, he should be encouraged to reconsider his stance against behavioral counseling and offered a referral to behavioral health for care coordination.

He may choose to discontinue naltrexone treatment after several months of abstinence or well-controlled alcohol use that falls within NIAAA guidelines. As with all patients, routine screening for problem alcohol use should be incorporated into future annual health surveillance, and naltrexone treatment can be reinstituted when indicated.

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Rheumatology in Primary Care

A Pharmacology Review

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Pain and inflammation characterize the story of rheumatology. The Centers for Disease Control and Prevention (CDC) estimates that musculoskeletal and connective tissue diseases account for more than 8% of ambulatory office visits in the United States annually; most of these visits are associated with osteoarthritis.[1]

The use of prescription and over-the-counter (OTC) analgesics is ubiquitous, and non-steroidal anti-inflammatory drugs (NSAIDs) make up 5% to 10% of all medical prescriptions. Thus, medical providers must be familiar with their use.[2] In addition, the development of biologic drugs in addition to the disease-modifying antirheumatic drugs (DMARDs) for more autoimmune diseases requires increased familiarity with regard to indications and side effect profiles by all clinicians.

The following brief overview provides history, pharmacology, and guidelines for the most commonly used medications in the management of rheumatic disease.

PHARMACOLOGY REVIEW BY MEDICATION TYPE

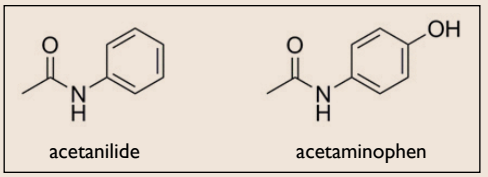
Acetaminophen

The mechanism of action of acetaminophen is not entirely clear but is thought to occur by blocking cyclooxygenase (COX) enzymes, decreasing prostaglandins, blocking serotonin neurotransmitters in the central nervous system, and modulating the endogenous cannabinoid system. In contrast to NSAIDs, acetaminophen does not have an anti-inflammatory effect. Acetaminophen toxicity is caused by the reactive metabolite *N*-acetyl-*p*-benzoquinone imine, which reacts with hepatocyte cellular proteins causing hepatic injury.

Of note, 50% of acetaminophen overdose events are unintentional and can be caused by chronic doses of only 4 g/day. The antidote for toxicity is *N*-acetyl cysteine, which must be given within eight hours of ingestion. While liver toxicity is the most serious adverse reaction, nausea, drowsiness, and hypersensitivity reactions may also occur. Unfortunately, inefficacy of acetaminophen for chronic musculoskeletal pain is a major drawback.

HISTORICAL SNAPSHOT
Acetaminophen

In the 1880s, two chemicals borrowed from the dye industry — acetanilide and phenacetin — were marketed as anesthetics for headaches. While useful, these chemicals caused methemoglobinemia. A compound discovered as a metabolite in the urine of people taking these drugs was concentrated and later synthesized for commercial use as acetaminophen.



NSAIDs

Understanding the mechanism of action of NSAIDs means understanding the concept of COX isoenzymes COX-1 and COX-2 and their varied physiologic functions. NSAIDs function by inhibiting COX enzyme activity to decrease the conversion of arachidonic acid into proinflammatory cytokines and thereby decreasing downstream pain signaling and other manifestations of inflammation including swelling and fever. COX-1 is constitutively expressed in most body tissues, whereas COX-2 is the inducible isoenzyme associated with pathologic states.[3]

The U.S. market offers many NSAIDs, but all the non-selective COX inhibitors carry the same basic risks. Gastrointestinal (GI) side effects of non-selective COX inhibitors most commonly include dyspepsia and heartburn but can also include gastric ulcers and perforation. COX-1 inhibition leads to reduction in prostaglandin levels and thus disruption in the gastric mucosal barrier, which makes surface cells of the stomach and esophagus vulnerable to gastric acid.

Additionally, factors that increase the risk of GI

complications include concomitant therapy with other medicines such as antiplatelet agents, anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors (SSRIs). Age greater than 65 years, severe illness, concomitant alcohol and tobacco use, history of peptic ulcers, and *H. pylori* infection also increase the risk.[4]

Several NSAIDs were formulated to selectively inhibit COX-2 in an effort to reduce the negative GI effects of non-selective COX inhibitors. Although rofecoxib and valdecoxib are no longer on the market due to increased risk of cardiovascular (CV) events, celecoxib remains on the market as the primary COX-2 selective agent. Celecoxib may serve a role in patients who require an NSAID and have high GI risk and relatively low cardiovascular risk.

The Food and Drug Administration (FDA) issued a black box warning regarding increased risk of heart attack or stroke associated with any non-aspirin NSAID use. For anyone with CV risk factors, when NSAIDs cannot be avoided, the lowest effective dose and shortest duration of therapy should always be prioritized.

The third major category of risk associated with NSAID use is universal to both selective and non-selective agents. Renal dysfunction, peripheral edema, and hypertension can all result from inhibition of PGI_2 and PGE_2 production by the kidneys. As potent vasodilators, these prostaglandins ensure adequate kidney perfusion unless COX inhibition limits their production. NSAID use can be especially dangerous in older adults, patients with chronic kidney disease or diabetes mellitus, or patients taking medications that might affect kidney perfusion.

Topical NSAIDs provide an alternative to oral NSAIDs and are approved for osteoarthritis of the knee and hand. Their efficacy in older patients is 30% to 40% of oral formulations. As an example, diclofenac gel is available in 1% concentration in the United States. Topical NSAID use is associated with 5% to 10% of the systemic exposure incurred by oral agents.[4] For hand osteoarthritis, topical NSAIDs rather than oral NSAIDs are preferred in persons older than 75 years.

Tramadol

Tramadol is a synthetically derived opioid with partial mu-opioid receptor binding. Tramadol provides additional pain management options for people with contraindications to NSAIDs, when other therapies are ineffective, or when no surgical options are available for patients with severe pain. Studies, however, suggest that tramadol use in a postoperative setting is more likely to result in chronic opioid use, thus providers should exercise caution if using this medication.[5]

HISTORICAL SNAPSHOT NSAIDs

- Hippocrates (400 BC) was known to make willow leaf tea as part of his medical practice. Research later showed that salicin in willow tree bark converts to salicylic acid *in vivo* to provide analgesia through COX enzyme inhibition.
- Acetylsalicylic acid (ASA) was synthesized and named aspirin in 1899.
- In 1961, Stewart Adams developed ibuprofen in hopes of curing rheumatoid arthritis.[4]
- Thirty billion OTC doses of NSAIDs and 70 million prescriptions are processed annually in the United States.[4]

Photo by peter-rabbit, via Flickr, CC BY-NC 2.0 DEED.

Duloxetine

Recent meta-analyses demonstrate some patients with osteoarthritis and fibromyalgia can benefit from the use of antidepressants such as duloxetine.[6,7] While the exact mechanism of action for duloxetine is unknown, it offers a wide array of indications through serotonin and norepinephrine reuptake inhibition, along with weak inhibition of dopamine reuptake.

Current FDA-approved indications include major depressive disorder, diabetic peripheral neuropathy, generalized anxiety disorder, fibromyalgia, chronic low back pain, and chronic musculoskeletal pain from osteoarthritis. Like other serotonin reuptake inhibitors, duloxetine may increase the risk of short-term suicidality and mania. The risk of suicidal thoughts and

behaviors is greatest in patients younger than 24 years old. Nevertheless, antidepressants like these decrease suicidal thoughts and behaviors in patients older than 65 years.[8]

Common side effects include nausea, dry mouth, headache, and fatigue. Providers should avoid rapid discontinuation of duloxetine due to potential for withdrawal symptoms. A gradual taper is advised when discontinuing this medication.

Disease-Modifying Antirheumatic Drugs

DMARDs are divided into several distinct categories by virtue of their synthesis and mechanisms of action (see Table 1). Conventional synthetic DMARDs (csDMARDs) include the traditional first-line therapies for disease-modifying activity: hydroxychloroquine, methotrexate, sulfasalazine, and leflunomide.

Hydroxychloroquine (HCQ) — used in anti-phospholipid syndrome, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) — works as an immunomodulator by inhibiting toll-like receptor signaling and inhibiting cyclic GMP-AMP synthase (cGAS) DNA binding to decrease pro-inflammatory cytokine expression. Of note, maculopathy may be seen in patients using HCQ and may lead to irreversible vision loss. This typically happens with HCQ dosing >5 mg/kg as is common for SLE patients. Other unique side effects include the development of blue-grey discoloration to skin, vivid dreams, and auditory hallucinations.

Table 1. Disease-Modifying Antirheumatic Drugs (DMARDs)

Class	Drug	Indication	Comments
Conventional synthetic (csDMARD)	hydroxychloroquine	Preferred initial therapy for DMARD-naïve patients with low disease activity.	Low cost and less bloodwork monitoring required; risk of retinal toxicity.
	methotrexate	Preferred initial therapy for moderate-to-severe disease and foundation of treatment for any DMARD combination.	Hold during acute hospitalization, infection, or antibiotic use; not recommended in the setting of liver or kidney disease.
	sulfasalazine	Alternate DMARD for initial rheumatoid arthritis (RA) management.	Excreted in bile and split into active metabolites by bacterial enzymes in large intestine.
	leflunomide	Recommended after trial of other csDMARDs.	Teratogenic; hepatotoxic, reverse toxicity by use of cholestyramine to disrupt enterohepatic recirculation.
Targeted synthetic (tsDMARD)	Janus Kinase inhibitors (baricitinib, tofacitinib, upadacitinib)	For moderate-to-severe RA after failure of tumor necrosis factor alpha (TNF-α) inhibitors.	Oral formulation, increased CV risk; avoid in patients with blood clotting disorder; increased risk of cancer; risk of infection.
Biologic (bDMARD)*	TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)	Generally, first-line biologic, in combination with methotrexate for moderate-to-severe disease (including RA, psoriatic arthritis, plaque psoriasis, inflammatory bowel disease) for corticosteroid sparing and reduced disease burden.	Avoid in patients with certain blood and solid tumor cancers; risk of infection.
	T-cell costimulatory inhibitor (abatacept)	For moderate-to-severe RA.	Possible lower infection risk compared to other biologics.
	IL-6 receptor inhibitors (sarilumab, tocilizumab)	For RA and temporal arteritis.	Avoid in patients with GI perforation.
	Anti-CD20 antibody (rituximab)	RA and antineutrophilic cytoplasmic antibody associated vasculitis, antiphospholipid syndrome, dermatomyositis, and lupus small vessel vasculitis.	Up to 25% incidence of reaction on initial transfusion, with decreased severity during subsequent transfusions.

** Considerations for Use of Biologics*

- *All options are expensive.*
- *Pretest for HIV, tuberculosis, and hepatitis B and C.*
- *Avoid live vaccines.*
- *Associated with increased risk of infection.*
- *Discontinue use during acute infection or hospitalization.*

As a dihydrofolate reductase inhibitor, methotrexate disrupts conversion of folic acid to tetrahydrofolic acid, depleting purines and nucleic acid synthesis, which results in immune cell apoptosis and decreased T-cell proliferation. Folic acid supplementation is important for patients taking methotrexate (MTX) as it reduces side effects during use. Long-term monitoring must be established for any patient taking MTX.

Both acute and chronic toxicities can cause liver function test abnormalities, bone marrow suppression, and increased risk of infection. Patients should not take MTX during any hospitalization, acute infection, antibiotic use, or when the glomerular filtration rate (GFR) is <30.

A first-line therapy in Europe, sulfasalazine can be used for both RA and inflammatory bowel disease, although the active metabolite is different depending on the target disease. After metabolism by gut bacteria, the active metabolites sulfapyridine and 5-aminosalicylic acid exhibit their effects.

Leflunomide produces an anti-inflammatory effect by disrupting T-cell progression into the S phase of the cell cycle and by blocking pyrimidine production. This medication is notable for a long half-life of 15 days and may remain detectable for two years after delivery. Because leflunomide is hepatotoxic, it should be avoided with any history of liver disease. Other side effects include nausea, vomiting, and fetal toxicity.

As with many aspects of rheumatology management, a systematic and stepwise approach with clearly defined goals is preferred (see Fig. 1). A treatment goal of low disease activity is realistic in chronic autoimmune disease such as rheumatoid arthritis. Every strategy must include consideration of side effects, costs, and patient preferences.

HISTORICAL SNAPSHOT DMARDs

- The natural precursor of hydroxychloroquine (HCQ), quinine has been reported to have been used by Incan descendants to cure a febrile illness in around 1630.[9]
- Chloroquine was introduced to rheumatology after soldiers given antimalaria prophylaxis in World War II were noted to have improvement in rashes and autoimmune arthritis.
- When Rex Hoffmeister began using methotrexate (MTX) to treat rheumatoid arthritis (RA) in the 1970s, the rheumatology community was hostile toward using an anti-cancer drug in a "benign disease." However, the original placebo-controlled trials of the 1980s pushed MTX to the forefront of pharmacotherapy for rheumatoid arthritis.[10]

Corticosteroids

Corticosteroid medications are among the most prescribed medications for treating pain in common rheumatic conditions. These powerful anti-inflammatory drugs inhibit pain by altering cytokine production; corticosteroids bind to intracellular receptors and change transcription at the DNA level. The change in cytokine expression leads to apoptosis of immune cells that would otherwise drive the inflammatory response.

In the short term, corticosteroids provide excellent relief. Early side effects include hyperglycemia, sleep disturbance, peripheral edema, weight gain, and

Fig. 1. Considerations for increasing tolerability and efficacy of methotrexate.

- Methotrexate is started at lower dose with titration toward full dose depending on laboratory and symptom monitoring side effects.
- Split weekly dosing over one 24-hour period results in higher absorption at the doses of 15 mg to 20 mg.
- Trial weekly injections if oral therapy is not tolerated or effective.
- Increase the dose of folic acid supplementation to mitigate methotrexate side effects.
- Alcohol use is discouraged in the setting of MTX use.

Fig. 2. Considerations for use of glucocorticoids in rheumatic disease.

- Consider a DMARD in place of glucocorticoids anytime more than three months of maintenance therapy is expected.
- Initiate a DMARD or switch to a separate class for anyone requiring a glucocorticoid to maintain their disease management target.
- Consider glucocorticoids, NSAIDs, or colchicine for treatment of acute gout flares as monotherapy for mild-to-moderate pain, or a combination of glucocorticoids with NSAIDs or colchicine for severe polyarticular disease.

increased appetite. Additionally, for locally injected corticosteroids, dermis atrophy and ligament weakness are concerns.

With long-term use, corticosteroids cause significant risk of multi-system degradation, including disruption of normal skin, hair, and bone structures; endocrine disruption causing adrenal insufficiency, Cushingoid features, or diabetes; and osteoporosis and increased risk of infections due to chronic immunosuppression. (See Fig. 2 on page 115 for considerations of glucocorticoid use in RA.)

Colchicine

Borrowed from cancer therapy, colchicine is an inhibitor of microtubule function in the cell, leading to impaired cellular trafficking which causes impaired neutrophil function and reduced pro-inflammatory cytokines. Colchicine deserves additional attention due to its versatile utility in the setting of multiple arthritic complaints. While often used in the setting of acute gouty arthritis, colchicine is also indicated for management of pain with familial Mediterranean fever or pericarditis.

Acute gout is an excruciatingly painful, yet common form of inflammatory arthritis. Management requires fast and effective pain control initiated within 24 hours of onset of an acute gout attack, and as soon as symptoms present if possible. Colchicine, along with other options such as NSAIDs and corticosteroids, offers a unique opportunity to treat gout effectively.

Patients with an established diagnosis of gout should have a treatment plan for acute gouty attack on hand, with written instructions and medication available at home.

Xanthine Oxidase Inhibitors

Initiation of urate-lowering therapy is considered in patients with two or more episodes of gout within one year, in patients with a severe initial episode, or in patients with polyarticular gout. Prevention of acute gouty arthritis is achieved through disruption of purine synthesis, which decreases serum uric acid levels.

The xanthine oxidase inhibitors, allopurinol and febuxostat, are first-line therapies. Since uric acid can precipitate into crystals at serum levels >6 mg/dL, maintenance therapy should be titrated to keep uric acid below this level. A lower level (<5 mg/dL) may be targeted.

HISTORICAL SNAPSHOT
Colchicine

- Derived from the corms of the *Colchicum autumnale* plant, colchicine has been used since ancient times, with the Egyptian *Ebers Papyrus* showing evidence of its use as far back as 1500 BC.[11]
- Although in the 1800s it became an "orphan drug" for many years, colchicine finally received FDA approval in 2009.[11]

Providers may consider initiating allopurinol at 100 mg and titrating to a maximum dose of 900 mg daily. The median dose of allopurinol necessary to keep uric acid levels <6 mg/dL is 450 mg daily. Allopurinol can be safely utilized when the creatinine clearance (CrCl) is as low as 10 mL/min.

An important consideration should be given to anyone whose family history suggests increased risk of developing hypersensitivity reaction to use of allopurinol. HLA-B*5801 allele testing should be performed in anyone considered at risk prior to initiating allopurinol therapy.

A more expensive alternative, febuxostat, was initially developed for use in chronic kidney disease; however, its cost and limited dosing options, along with a side effect profile similar to allopurinol, make febuxostat a less compelling alternative. Concerns regarding an increased

risk of cardiovascular events with this medication are still being investigated in post-marketing studies.

Second-Line Urate-Lowering Therapies

Probenecid lowers serum uric acid by blocking uric acid transporters in the renal tubules, resulting in uric acid excretion. This mechanism requires adequate kidney function (CrCl >30 mL/min) to be most effective. As a second-line therapy, probenecid is used in combination with an appropriately dosed xanthine oxidase inhibitor if serum urate levels are not at target. Patients should avoid probenecid use in acute gouty arthritis as it may exacerbate symptoms.

Pegloticase is reserved for severe gouty arthritis in patients refractory to appropriate dosing of other urate-lowering agents.

COLLABORATION MOVING FORWARD

Until now, many pharmacotherapies for rheumatologic disease have been non-specific in their use to attenuate inappropriate immune activity. Now targeted immune modulators — recently approved or in the process of development — for psoriatic arthritis, vasculitis, systemic lupus, and other less common autoimmune diseases require increased attention and continued study.

Newer infusions, for example, may not appear on standard medication lists in the electronic medical record, and a diagnosis of a rheumatologic condition should be a cue to all providers to review what therapies patients may have received.

Curiosity and clear communication among providers should remain standard practice. We should not hesitate to reach out to colleagues, to include rheumatology and pharmacy consultants, regarding questions about medications and their side effects.

CONCLUSION

Ancient remedies of chewing on *Colchicum* root or drinking willow leaf tea led to modern derivatives that remain in use today. Borrowed medications and broad strokes against autoimmune disease are being replaced by targeted immune modulators. Given the high prevalence of rheumatic disease, all clinicians should be familiar with available analgesic and anti-inflammatory pharmacotherapies.

ACKNOWLEDGEMENT

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BOOK REVIEW


Hamblin


Lawson

Sentenced to Science: One Black Man's Story of Imprisonment in America

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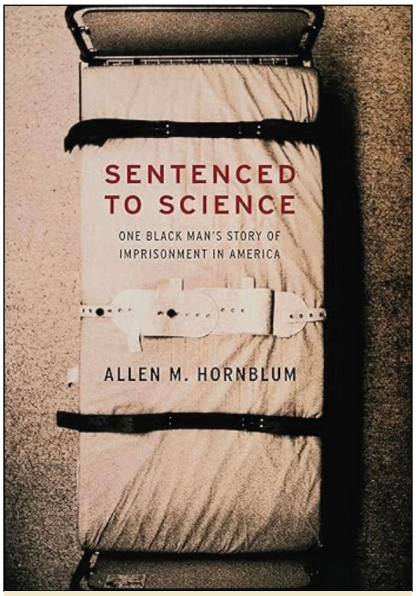
Sentenced to Science: One Black Man's Story of Imprisonment in America by Allen Hornblum was published in 2007 by The Pennsylvania State University Press. This 200-page paperback chronicles the wide spectrum of abusive medical experimentation endured by Edward Anthony during his time at Philadelphia's Holmesburg Prison in the 1960s. It further recounts the experimentation of the infamous Dr. Albert Kligman between the 1950s and 1970s.

Blending firsthand testimony by Edward "Yusuf" Anthony with the author's voice, which provides contextualization and perspective, *Sentenced to Science* provides an important account of abuses in the name of scientific and medical discovery, with telling insight regarding informed consent and our criminal justice system. Hornblum is a Philadelphia-based author, journalist, former criminal justice official, and political organizer. He has written eight nonfiction books, and lectures at Temple and Drexel universities and to audiences of medical scholars and laypeople alike.



By Allen M. Hornblum,
University Park, Penn State Univ. Press, 2013,
232 p, 26.95 paperback

Hornblum writes that Kligman, who was invited to Holmesburg Prison in 1951 to treat an outbreak of athlete's foot, gained exclusive experimental use of inmate bodies through the 1950s and 1960s. He tested 153 experimental drugs between 1962 and 1966 alone. Through his research on prisoners, Kligman — a University of Pennsylvania dermatologist — became well known for developing Retin-A to treat acne, and for contributing to breakthroughs in dermatology in the areas of seborrheic dermatitis, ringworm, and alopecia.

Holmesburg Prison — nicknamed the "Terrordome" — was operated by the City of Philadelphia and the Pennsylvania Department of Prisons from 1896 to 1995, when it was decommissioned. It was the site of decades-long dermatologic, pharmaceutical, and biochemical weapons research conducted on prisoners for at least 35 major companies.

As most researchers are now aware, we must study our history. Reading about and understanding the Nuremberg Code (10 points that guide medical experimentation that resulted from the Nuremberg Trial after World War II) and the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* provide an introduction for reflection on the principles of medical ethics — specifically: autonomy, beneficence, nonmaleficence, and justice. The accounts of events at Holmesburg Prison during the 1960s add homegrown background for clinicians and researchers participating in human trials or obtaining informed consent in any setting.

Sentenced to Science, like the latter texts, can leave medical students and practicing physicians challenged, reflective, and cogitabund. A gut-wrenching yet elucidative account of medical experimentation done in Northeast Philadelphia from 1951-1974, this book centers the narrative of Edward "Yusuf" Anthony, who recounts his experiences as the subject of medical testing while incarcerated.

BOOK SUMMARY

Early chapters paint the scene of Anthony's upbringing and changes in the population in the Strawberry Mansion section of North Philadelphia, where he was raised, throughout the end of the 1950s. On page 15, Hornblum writes:

> As a child growing up in the heart of the jungle, Eddie Anthony was understandably ignorant of the shifting demographics and changing socioeconomic fortunes affecting his community. The flight of white residents to Northeast Philadelphia and the suburbs and the gradual demise of the area's industrial base were beyond his comprehension.

He recounts wanting to break away from the strict upbringing of his Baptist parents, more identifying with "guys who were cool and doing cool things."

By the time he was 16 or 17 years old, Anthony was cutting school, smoking marijuana, drinking alcohol as well as cough syrup with codeine, and had become addicted to heroin. It wasn't long before he ended up in prison, and he would spend much of his adult life in and out of incarceration. Shortly after arriving at Holmesburg Prison, Anthony's experience with unethical medical experimentation began.

Anthony entered Holmesburg Prison in 1964. He quickly learned that the people wearing white coats, explaining the studies, and obtaining his consent were not physicians but fellow inmates. When he and others developed complications from the studies, they were unable to access medical evaluation, treatment, or care. Over the course of 16 chapters, the author, through Anthony's words, tells of Anthony's time at Holmesburg Prison during the mid-1960s, during which he participated in several studies and suffered many complications. At that time, men who were incarcerated were frequently subjected to phase 1 drug trials, including exposure to detergents and applications of agents such as dioxin to the skin.

Anthony relates that days after arriving, he enrolled in a study meant to determine if Johnson & Johnson bubble bath was harmful to someone with open wounds. Participating in a study seemed like an easy way to pass the time during his prison stay and earn $37 over the course of three weeks. Yet he soon came to regret his consent, as researchers removed his skin, layer by layer, by placing adhesive tape on his back and then ripping it away, again and again, in the same spot.

Next, a solution was applied to these areas with gauze secured with tape; alcohol-based spray was then applied. Knowing he would only be paid if he withstood the entire test, he had no choice but to allow this process to be repeated daily for weeks. He explains:

> It was like something was crawling under my skin. Under my arms and between my legs it's getting real hot. I'm moaning. My cell mates can't do anything for me, and I'm keeping them from getting any sleep at night. I'm thinking the whole time, what the hell did I get myself into? I'm blaming my cell partners, the damn doctors, myself, I don't know who to blame.

Anthony recounts his recovery from this experiment and subsequent enrollment in others, from which he developed many complications. From backroom hemorrhoid treatment without follow-up care to developing such frightening physical effects from "treatments" that he scared fellow inmates and found himself sent to solitary confinement, it is a harrowing account. He was eventually hospitalized in Philadelphia, found Islam, and although he was in and out of prison for most of his adult life, he finally ended a state prison term that marked the end of his journey with illicit drugs and corrections facilities.

The final chapter of *Sentenced to Science* recounts how the unethical experimentation at Holmesburg Prison came to light and what happened in the immediate aftermath. Interestingly, knowledge of the abuses first became widespread due to reports in Hornblum's book *Acres of Skin*, which detailed Kligman's gruesome work. The book itself was a sensation when it was published in 1998, yet many former prisoners were caught off guard.

So it was for Edward Anthony, who, in the Spring of 1998, heard details of his life story being described, along with those of other Holmesburg Prison victims, on the six o'clock news. Survivors of the Holmesburg experiments began to meet for discussion and eventually organized to bring suit against the City of Philadelphia and the University of Pennsylvania. Responses by Dr. Kligman included comments that his research "was in keeping with the nation's standard protocol for conducting scientific research at that time."[1]

Sadly, the suit did not result in restitution or remuneration to the victims. The statute of limitations had passed, and the burden of proving the long-term effects these men faced proved to be too high. Victims were never compensated. Even though Anthony suffers anxiety associated with public speaking, he has subsequently shared his experiences with medical students

and other learners, through the coordination of the author. It is unclear whether or how he has been paid for this work.

As with all coauthored texts, readers should be cautious about the framing of the story and the influence of the journalist's own experiences and background. Nevertheless, readers will empathize with not only Anthony's self-discovery, but how America's eyes were opened when the curtains were drawn back to reveal the horrors of Holmesburg Prison.

The United States has an incarceration rate up to 10 times higher than countries like Canada, France, and the U.K.; in fact, we have the highest rate in the world.[2] These are our brothers and sisters. Yet the United States is the only democracy in the world that still does not have an independent authority to monitor the conditions, health, and safety of our prisons and their inhabitants.

By reading *Sentenced to Science: One Black Man's Story of Imprisonment in America,* medical professionals everywhere will gain new perspective on the nuances of informed consent, as well as how collective experience can contribute to community distrust of establishment and medical institutions.

RESOURCE LIST FOR CONTINUED LEARNING

Video about *Sentenced to Science*
https://english.news.cn/northamerica/20230208/540e8eb200104b46b40d6e531db73900/c.html

Edward Anthony's Testimony before Congress
https://www.legis.state.pa.us/WU01/LI/TR/Transcripts/1999_0118_0011_TSTMNY.pdf

The Problem with Race-Based Medicine, Dorothy Roberts
https://www.youtube.com/watch?v=KxLMjn4WPBY

Medical Apartheid
by Harriet Washington

Carte Blanche: The Erosion of Medical Consent
by Harriet Washington

Killing the Black Body
by Dorothy Roberts

Body and Soul: The Black Panther Party and the Fight Against Medical Discrimination
by Alondra Nelson

Fatal Invention
by Dorothy Roberts

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PHOTO QUIZ FROM URGENT CARE

Love Hurts

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CASE HISTORY

A 75-year-old male presents to Urgent Care stating that he has had a rash on his hand for two weeks. It is not pruritic, and it does not burn. The patient reports that he usually cuts rose bushes for his wife without gloves and believes that he pricked the fingers of his right hand when removing the thorns with his clippers. He is confident that he completely removed a rose thorn that was stuck inside his middle finger.

The rash has not spread, and he is not having any systemic symptoms. He has been putting topical Neosporin® on the open wounds for what he presumes is an infection, but the discoloration has not significantly improved. The patient describes a history of Raynaud's phenomenon — his fingers blanch when his hands are cold.

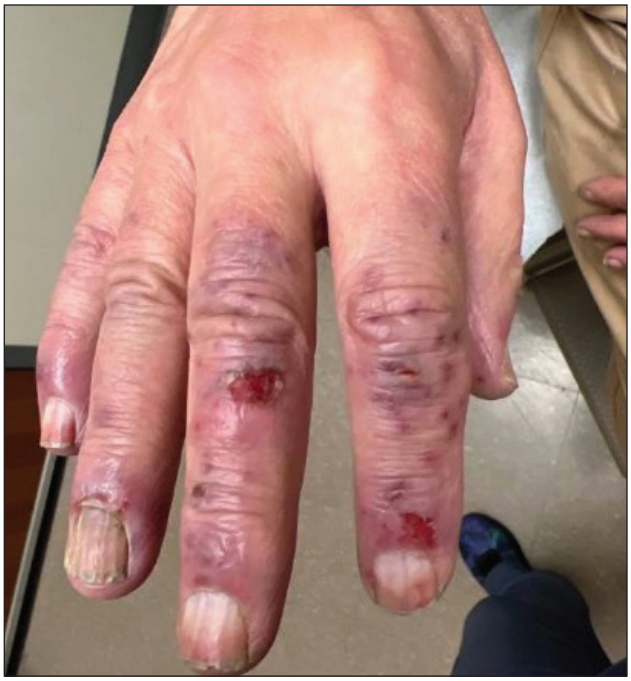

Fig. 1. Photo of patient's right hand in Urgent Care setting.

His history is otherwise remarkable for a long record of eczema on his hands for which he uses over-the-counter emollients. A photo of the patient's right hand is taken for the chart (see Fig. 1).

QUESTIONS

1. What is another popular name for this skin infection?
2. What is the most common form of this type of infection?
3. What is usually the first symptom?
4. What is the best diagnostic test for this disease?
5. What is the suggested treatment approach in this case?

ANSWERS

1. Sporotrichosis is also known as "rose gardener's disease" because it is caused by a fungus that lives in soil and on plant matter such as rose bushes, sphagnum moss, and hay.
2. Cutaneous sporotrichosis is the most common form of this infection, generally on the hand or arm after touching contaminated plant matter. Other forms are lymphocutaneous, pulmonary, and disseminated sporotrichosis.
3. Cutaneous sporotrichosis manifests with small, painless bumps that develop anywhere from one week to three months after exposure to the fungus.
4. The most useful test is culture from tissue biopsy of the infected area. Blood tests can assist in systemic sporotrichosis, but they are not relevant in cutaneous skin infections.
5. Itraconazole 200 mg by mouth daily for three to six months is the most common treatment; supersaturated potassium iodide (SSKI) can be used as well. During pregnancy, infectious disease consult may be warranted; oral terbinafine or amphotericin B can be considered.

DISCUSSION

Sporotrichosis is caused by the fungal genus *Sporothrix,* usually *Sporothrix schenckii.*[1] Cutaneous and subcutaneous infection is common; immunocompromised patients may be at risk for infection in other sites, including the lungs or brain. Activities during which patients may experience inoculation of soil under the skin, such as gardening, put patients at risk for this infection.[2]

In immunocompromised hosts, the infection can disseminate hematogenously to affect other organ systems (e.g., central nervous system). Extracutaneous forms of sporotrichosis may present in isolation or as a manifestation of more disseminated disease.[3] Symptoms of extracutaneous sporotrichosis can be subtle, and diagnosis may be delayed.

Lymphocutaneous sporotrichosis is the most common form seen in clinical practice and presents as nodular lymphangitis. A patient is usually otherwise healthy, with an outdoor job or hobby (e.g., landscaping, gardening).[4] Days to weeks after inoculation of the fungus, a cutaneous papule develops at the site. This primary lesion may ulcerate or remain nodular and erythematous; drainage from the lesion is rarely purulent and usually serosanguinous and odorless.[2]

Similar lesions may follow along the lymphatic channels proximal to the first lesion, a finding called sporotrichoid spread or nodular lymphangitis. Pain is generally mild, and there are usually no systemic symptoms. Self-resolution is rare.

When sporotrichosis is suspected, culture from tissue biopsy (gold standard), sputum, body fluids, or aspirated material from a skin lesion should be collected. Growth may take days to several weeks; a positive culture is diagnostic. Although special stains (e.g., methenamine silver stain) can be performed for histopathology, they are often negative because the number of organisms required to cause disease is small.[1]

In a study of 645 patients in Brazil, itraconazole was found to be highly effective at treating cutaneous sporotrichosis.[5] Six hundred ten patients (94.6%) were cured with itraconazole (50 mg to 400 mg/day): 547 with 100 mg/day, 59 with 200 mg to 400 mg/day, and four children with 50 mg/day. Approximately 20% of patients experienced adverse events, most commonly nausea and abdominal pain.[5]

Thus, patients should be treated with itraconazole 100 mg to 200 mg by mouth daily unless there are contraindications. If patients are not responding, doubling the initial dose to a maximum of 400 mg per day may suffice. Consideration of an infectious disease consultation may be warranted.

Children may follow a similar antifungal regimen of oral itraconazole 6 mg/kg to 10 mg/kg up to a maximum dose of 400 mg daily. If this is not well tolerated, a liquid saturated solution of potassium iodide may be used: one drop in milk or juice three times daily and increased every seven days as tolerated to a maximum of one drop per kg or 40 to 50 drops three times daily, whichever is lower, may be appropriate.

Patients should not use azoles during pregnancy.[2] Again, an infectious disease consult may be warranted as a lipid formulation of amphotericin B (3 mg/kg to 5 mg/kg per day intravenously) may help. One small case series from Japan demonstrated that pocket warmers and infrared and far infrared rays could help cure cutaneous and lymphocutaneous lesions.[6]

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SPOTLIGHT ON CLINICAL RESEARCH

Success Stories, What's Next, and How You Can Help

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Kabagambe


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In June 2022, the Penn Medicine Lancaster General Health Research Institute welcomed Dr. Edmond Kabagambe to the health system as the inaugural vice president of Research Administration. In the time since his arrival, research across LG Health has become more cohesive and streamlined with a strong focus on collaboration both internally and with other Penn Medicine entities. In the following article, Dr. Kabagambe shares examples of what we have been able to achieve and what exciting opportunities await in the future.

Over the past year, many physicians accepted the call to serve as principal investigators (PIs) or sub-investigators (Sub-Is) for clinical research. This role comes with many responsibilities, including completing or renewing CITI (Collaborative Institutional Training Initiative) certifications, meeting with the study team, reviewing and signing off on all study updates, and more. Among the 347 unique CITI certifications in Fiscal Year 2023 (FY23), 53 were from physicians and 26 were from advanced practice providers (APPs).

We recognize that a patient is more likely to consent to participate in a study if they hear about it from a provider rather than from any other member of the study team. Enrollment has seen a marked increase as a result of the great engagement of CITI-certified physicians, APPs, nurses, pharmacists, and other researchers. In addition to being instrumental in enrollment efforts, CITI certifications also allow us to maintain a high standard of regulatory compliance.

This excellence in regulatory compliance was highlighted prominently in the Association for the Accreditation of Human Research Protection Programs (AAHRPP) reaccreditation of the LG Health Human Research Protection Program (HRPP), a months-long process that required inter- and intra-departmental efforts, policy revisions, and interviews coordinated by Jonathan Derr, administrative director of the Research Institute. Our HRPP has been AAHRPP-accredited since 2015, signifying that the HRPP meets the most rigorous standards for maintaining the safety of research participants.

Recent achievements from providers, pharmacists, nurses, research coordinators and assistants, and the research administration team are shown in Table 1. For example, nearly 1,000 unique patients were consented and enrolled in clinical research studies. Compared to FY22, the number of new patients in non-cancer clinical studies increased by 38% in FY23, and

Table 1. Overview of LG Health Research Metrics in Fiscal Year 2023

Number of Patients in Research Studies *(enrolled and in follow-up)*:	**993**
Percentage of Minorities in Non-Oncology Clinical Studies:	**7.2**
Percentage of Minorities in Oncology Clinical Studies:	**5.5**
Number of Enrolling Studies:	**35**
Number of Studies in Start-Up *(not yet approved by the Institutional Review Board)*:	**10+**
Number of Studies in Feasibility Assessment *(first step of start-up process to ensure patient population and necessary resources are in place to conduct the research)*:	**10+**

enrollment of minorities increased from 5.8% to 7.2% in the same period.

While these advancements are certainly worth celebrating, we are also excited about the future of research. There are still many departments and patients that could benefit from clinical research. One of our goals for FY24 is to continue to expand clinical research across service lines and departments, while simultaneously increasing patient diversity by race, ethnicity, sex, and other demographics. We continue to work closely with the Diversity, Equity & Inclusion department to align our goals and ensure respect and safety for research participants.

We are starting up several new studies that will enroll patients from rural and suburban practices to afford residents in those areas the opportunity to benefit from clinical research. These include studies on postpartum depression, diabetes, health misinformation, and more.

One simple way to facilitate research at LG Health is to encourage patients to enroll in MyLGHealth and opt in to learn more about research studies for which they might qualify. This allows the research team to reach patients wherever they are.

Research is truly a team effort; we could not do what we do without the support, resources, and efforts of investigators, statisticians, pharmacists, the Information Services team members, and countless others. We look forward to welcoming more researchers to our efforts and cannot wait to see what opportunities the future holds for research at LG Health and beyond.

To learn more about the cutting-edge research taking place at LG Health, visit lancastergeneralhealth.org/health-care-professionals/research-institute.

If you are interested in becoming a research investigator, contact the Research Institute via email at LGHResearch@pennmedicine.upenn.edu.

Active Clinical Studies at Lancaster General Health

A complete list of active clinical studies at Penn Medicine Lancaster General Health is available online.

To access the most current list, scan the QR code at right ➔ or find the link on the Resources/Links page at JLGH.org.

To make a referral to any study on the list, call the LG Health Research Institute at 717-544-1777.

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Recommendations from the American Society for Clinical Pathology

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The American Board of Internal Medicine (ABIM) Foundation this summer completed its Choosing Wisely initiative, launched in 2012 as a campaign "to spark conversations between clinicians and patients about what tests, treatments, and procedures are needed — and which ones are not." Since then, more than 80 specialty societies shared 700-plus recommendations of tests and treatments they said were overused or unnecessary; this journal published 42 articles sharing many of those recommendations.

Although ABIM no longer maintains and makes the recommendations available via their website, I will work with *JLGH* to continue to offer information to help readers in their daily practice of medicine. We will review past recommendations and offer new ones where available.

This issue marks my 43rd article on Choosing Wisely, with "Five or More Things That Physicians and Patients Should Question" from the American Society for Clinical Pathology. The Society has offered 35 recommendations over the years; the five below are new to this publication. Additional information on these items is available online at ascp.org/content/get-involved/choosing-wisely/choosing-wisely-ascp#.

RECOMMENDATIONS FROM THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY

1. Do not generally use swabs to collect specimens for microbiology cultures from the operating room. For optimal recovery of microbes, tissue or fluid samples obtained in the operating room should be submitted, when available. Swab specimens are not optimal for microbiology testing because, in this setting, alternative specimen types have greater specificity and are more likely to reflect the pathologic process being investigated. There is evidence that, in this setting, swabs do not offer benefit, and testing increases costs and does not provide higher quality care. Eliminating swabs when possible and only submitting tissue or fluid addresses these issues and results in a more effective use of laboratory resources and personnel.

2. Avoid thyroid stimulating hormone (TSH) screening in annual well-visits for asymptomatic adults, regardless of age. Testing is appropriate when patients are considered at risk or demonstrate subtle or direct signs of thyroid dysfunction upon physical evaluation. There is no evidence that finds routine TSH screening improves patient care.[1]

3. Do not perform urine cytology for routine hematuria investigation. This is costly and of limited clinical value as a first-line investigation for all patients with hematuria. A negative test does not rule out malignancy because this test has low sensitivity for diagnosing low-grade superficial urothelial malignancy. It is also impossible to localize a tumor based on urine cytology alone. Hematuria may require further invasive investigation, including upper urinary tract imaging and flexible cystoscopy.[2]

4. Do not order a Type & Crossmatch for patients undergoing procedures that have minimal anticipated blood loss, historically low fraction of transfusion use, and a low transfusion index (ratio of transfused units to patients). Appropriate use of blood component resources is critical to maintain adequate supply. The Type & Crossmatch is labor and reagent intensive, resulting in increased workload costs and increased inventory wastage. Each hospital's medical staff should have a maximal surgical blood ordering schedule, and it should be available to all members of the medical and hospital staff, upon request.[3]

5. Antiplatelet agent inhibition of platelet activity using platelet function or genetic testing should not be monitored. Evidence does not support the use of these laboratory tests to guide the dose of aspirin or clopidogrel in patients with so-called aspirin or clopidogrel "resistance." Study results do not provide support for the concept of changing antiplatelet therapy based on the results of platelet function monitoring tests. Thus, high on-treatment platelet reactivity (higher than expected platelet reactivity seen in patients receiving antiplatelet therapy) may be a non-modifiable clinical risk factor in patients treated with antiplatelet agents.[4]

Top Tips from Family Practice

GERMAN RESEARCHERS LINK AGE TO HIGHER AEROSOLIZED RESPIRATORY EMISSIONS

In a paper published in the *Proceedings of the National Academy of Sciences*[5] and reported by Medical Xpress,[6] researchers at the Universität der Bundeswehr München found unexpectedly high aerosolized respiratory emissions from people over 60 years old. The researchers detailed their findings after testing an improved method of measuring these emissions on 80 individuals.

Airborne respiratory diseases are transmitted by virus in respiratory particles. When a person breathes out, a high-speed stream of air rushes over the surface of the wet lining of the respiratory tract, and some of this moisture is aerosolized and carried out with the exhalation. Particles within the lining adhere to the exiting moisture that contains a mix of salts, proteins, mucus, and potential pathogens of bacteria and viruses.

Typically, the emission of aerosol particles can increase by more than a hundredfold from rest to peak exercise, and with the increase, the risk of infection can rise more than tenfold. The researchers found that subjects ages 60 to 76 years old emitted more than twice as many aerosol particles at rest and during exercise, and five times as much aerosol volume. This suggests that aerosol particle emission increases when the respiratory system ages.

At rest, the expired air of the older subjects contained an average respiratory aerosol particle concentration of 310 particles/L compared to 105 particles/L in younger subjects. The study found differences between elderly men and women, with elderly men emitting 210 particles/L compared to elderly women at 500 particles/L. While the elderly women had more than twice the particle load per liter of air, the elderly men ventilated 57% more volume than the elderly women, making the overall difference insignificant.

The age-related difference, however, was more significant during exercise, as the young group averaged 620 particles/L while the elderly group reached an average age of 2,090 particles/L.

While age significantly affected aerosol particle emission, gender and body mass index differences were not significant. The study highlights that one size may not fit all when planning mitigation measures, especially for indoor fitness facilities or elder care facilities during heightened infection waves or future pandemics.

AMERICAN HEART ASSOCIATION AND AMERICAN COLLEGE OF CARDIOLOGY ISSUE UPDATED CHRONIC CORONARY DISEASE GUIDELINE[7]

The latest clinical practice guideline for managing patients with chronic coronary disease (CCD) takes an evidence-based and patient-centered approach to care and includes key updates.

Developed by the American Heart Association (AHA), the American College of Cardiology (ACC), and other specialty societies, the 2023 guideline both updates and consolidates AHA/ACC guidelines previously published in 2012 and 2014 for the management of patients with stable ischemic heart disease. Among the key recommendations:

- Long-term beta-blocker therapy is no longer recommended for improving outcomes for patients with CCD in the absence of myocardial infarction (MI) within the past year, left ventricular ejection fraction (LVEF) ≤50%, or another primary indication for beta-blocker therapy. Either a calcium channel blocker or a beta-blocker is recommended as first-line antianginal therapy.
- Sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists are recommended for selected groups of patients with CCD, including individuals without diabetes, to improve outcomes.
- Statins remain first-line therapy for lipid lowering for patients with CCD. Several adjunctive therapies, such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, inclisiran, or bempedoic acid, may be used in select populations, although clinical outcomes data are not yet available for novel agents such as inclisiran and bempedoic acid.
- Shorter durations of dual antiplatelet therapy are safe and effective in many circumstances, particularly when the risk of bleeding is high and the ischemic risk is not high.
- The use of non-prescription or dietary supplements, including fish oil and omega-3 fatty acids or vitamins, is not recommended for patients with CCD, given the lack of benefit of reducing cardiovascular events.
- Revascularization is recommended in two scenarios: 1) for patients with lifestyle-limiting angina despite guideline-directed medical therapy and with coronary stenosis amenable to revascularization, with the goal of improving symptoms; and 2) for patients with significant left main disease or multivessel disease with severe LV dysfunction (LVEF

≤35%). With the goal of improving survival, coronary artery bypass grafting plus medical therapy is recommended over medical therapy alone for these high-grade lesions.
- Routine periodic anatomic or ischemic testing in the absence of a change in clinical or functional status is not recommended for risk stratification or to guide therapeutic decision-making for patients with CCD.
- Non-drug therapies, including healthy dietary habits and exercise, are recommended for all patients with CCD. When possible, patients should participate in regular physical activity, including activities to reduce sitting time and to increase aerobic and resistance exercise.
- Cardiac rehabilitation for eligible patients provides significant cardiovascular benefits, including decreased morbidity and mortality.
- Electronic cigarettes increase the odds of successful smoking cessation, but they are not recommended as first-line therapy, owing to lack of long-term safety data and risks associated with sustained use.

DIETARY SUPPLEMENTS FOR IMMUNE FUNCTION AND INFECTIOUS DISEASES

According to the National Institutes of Health (NIH), interest in dietary supplement ingredients that might enhance immune function and reduce the risk of infectious diseases is high, especially after the emergence of COVID-19.[8]

NIH notes that consuming adequate amounts of certain vitamins and minerals is important for proper immune function, and clinical deficiencies of these nutrients weaken immunity and can increase susceptibility to infections. Other ingredients such as botanicals and probiotics, whether provided through foods or dietary supplements, are not essential but might affect immune function.

The information that follows from NIH summarizes the effects of various dietary supplement ingredients on immune function and the risk of selected infectious diseases. Dietary supplement ingredients in each category are presented in alphabetical order. Some cases involve intravenous, enteral, or parenteral administration. Dietary ingredients administered by these routes are not classified as dietary supplements, but the information is included for completeness.

For detailed information on dietary supplements and COVID-19, refer to the NIH "Dietary Supplements in the Time of COVID-19" fact sheet.[9]

Vitamins and Minerals

Consuming a nutritious variety of foods helps maintain overall good health and a strong immune system. Obtaining adequate amounts of vitamins and minerals is also important for good health, and deficiencies of certain vitamins and minerals — including vitamins A, B_6, B_{12}, C, D, E, and K; folate; and copper, iodine, iron, magnesium, selenium, and zinc — might adversely affect immune function. Examples involving vitamins include:
- Folate deficiency affects thymus and spleen function and decreases T-lymphocyte levels, and vitamin B_{12} deficiency decreases the phagocytic capacity of neutrophils.
- Vitamin A deficiency is associated with increased susceptibility to infections, altered immune responses, and impaired ability of epithelial tissue to act as a barrier to pathogens.
- Vitamin E deficiency impairs humoral and cell-mediated immunity and is associated with reduced natural killer cell activity.

Examples involving minerals include:
- Copper deficiency is associated with altered immune responses and an increased risk of infection, especially in infants and older adults.
- Low magnesium status is associated with decreased immune cell activity, increased oxidative stress,

Museum Shares Historical Publications Online

As part of its mission to preserve the "rich medical heritage" of Lancaster County, the Lancaster Medical Heritage Museum shares its collection of historical medical publications online. Works offered include case studies and procedural overviews from local, national, and international journals, along with local advertisements, pamphlets, and more. Articles span a 55-year period, from 1946 through 2000, and are available at LancasterMedicalHeritageMuseum.org under the "Publications" pull-down menu. *JLGH* also hopes to reprint some of these in future issues.

"Though we have a varied and interesting compilation of articles available," says Alan Peterson, MD, a member of the *JLGH* Advisory Editorial Board who also serves on the Lancaster Medical Heritage Museum's Board of Directors, "we need your help. We do not believe our collection to be complete. If you are aware of other articles written in these years by LG Health staff, we'd love to hear from you." Email suggestions to museumlmh@gmail.com. The museum and its collection of over 11,000 medical artifacts is located at 410 N. Lime Street, Lancaster. Winter hours are Monday/Wednesday/Friday, 10:00 a.m. to 3:00 p.m. Admission is free to LG Health employees with a badge and children under 3, and $8.00 for all others.

and increased inflammation, including increased levels of some inflammatory cytokines, such as interleukin-6.
- Selenium deficiency might adversely affect immune response, as well as the pathogenicity of viruses.

The European Society for Clinical Nutrition and Metabolism states that low intakes or status of several micronutrients — including vitamins A, E, B_6, and B_{12}, as well as selenium and zinc — are associated with worse outcomes in patients with viral infections.

If needed, vitamin and mineral supplementation can boost intakes to recommended levels, but in the absence of deficiency, routine supplementation with micronutrients probably does little to prevent or treat specific infections.

NIH subsections describe research on the effects of dietary supplements containing more commonly studied vitamins and minerals — including vitamins A, C, D, and E, as well as selenium and zinc — on immune function.

FIVE STEPS TO HELP ADDRESS CLIMATE CHANGE

In a recent editorial in *Medpage Today*,[10] physician leaders at Northwest Permanente put out a call to physicians, clinicians, and health care delivery systems to help mitigate climate change. Statistics in the article highlight health care's contribution to the problem, including:

- American health care contributes 8.5% of all greenhouse gas emissions in the United States.
- Hospitals generate an enormous amount of nonrecyclable trash from single-use items that end up in landfills or incinerators.
- The gases emitted by one hour of anesthetic use are equivalent to driving a gasoline-powered car 250 miles, and some anesthetic gases, including nitrous oxide, can survive in the atmosphere for more than 100 years.

The article's authors, Leong Koh, MD, and Colin Cave, MD, write:

> Physicians are increasingly on the front lines of the crisis as ozone, smog, and particulate pollution from wildfires inflame lungs, exacerbate asthma symptoms, and worsen many health problems, such as diabetes, heart disease, cancer, and lung disease.
>
> As ... trusted advisors, we have a responsibility to reduce the climate impacts of the health care sector, including those of us who provide care ... During visits with patients, clinicians can signal that it is acceptable to talk about climate change, so patients feel comfortable bringing up climate-related concerns.

To address these concerns, the authors suggest we:

1. Advocate for policies that increase the primary care workforce and improve their well-being.
2. Move more care into the home through innovations like telehealth and remote patient monitoring.
3. Rethink supply-chain redundancy.
4. Make prudent use of medical supplies.
5. Ensure vulnerable communities are represented when planning policies.

Polls and studies have found that an individual's own physician is the most trusted advisor when it comes to health-related information and decisions. With that in mind, Drs. Koh and Cave conclude: "Let's use that influence for positive change."

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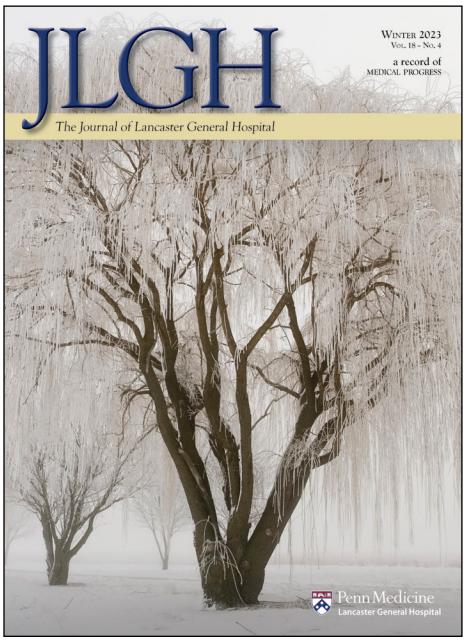

Cover photo of willow trees in winter by Steve Geer via iStock by Getty Images.

This issue of JLGH *features a pharmacology review of rheumatology in primary care. Read about the connection between willow tree bark and NSAIDs in the article beginning on page 112.*

INTERESTED IN WRITING FOR *JLGH*?

The following is a summary of the general guidelines for submitting an article to *The Journal of Lancaster General Hospital*. Details are located online at JLGH.org.

- Scientific manuscripts are typically between 2,500-4,500 words. Perspective articles are usually shorter, and photo quizzes average about 725 words plus illustrations.
- Medical articles should report research, introduce new diagnostic or therapeutic modalities, describe innovations in health care delivery, or review complex or controversial clinical issues in patient care.
- Reports of research involving human subjects must include a statement that the subjects gave informed consent to participate in the study and that the study has been approved by the institutional review board (IRB).
- Patient confidentiality must be protected according to the U.S. Health Insurance Portability and Accountability Act (HIPAA).
- The Journal of Lancaster General Hospital *does not allow chatbot tools such as ChatGPT to be listed as authors.* JLGH *editors warn authors that the use of these tools poses a risk for plagiarism with inappropriate use of citations, and we require that use of such tools be disclosed.*

Please contact the managing editor, Maria M. Boyer (717-544-8004), Maria.Boyer@pennmedicine.upenn.edu, to discuss submitting an article or for further information.

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EARN CME FOR READING THIS ISSUE OF *JLGH*

DID YOU KNOW, PHYSICIANS CAN EARN CATEGORY 2 CREDIT FOR READING *JLGH*?

American Medical Association Category 2 activities consist of self-directed learning or courses that have not been through a formal approval process. According to the Pennsylvania State Board of Medicine, this includes "learning experiences that have improved the care [physicians] provide their patients." Reading authoritative medical literature — like *JLGH* — is one such activity. More information and the Pennsylvania Board of Medicine CME Reporting Form are available at LGHealth.org/CME. Physicians can also log credit through their eeds account online.

← Scan to access your eeds account.

← Scan for more information and to access the Pennsylvania CME Reporting Form.

Lectures on Demand: DEA Licensing Requirements & More

The Medication Access and Training Expansion Act of 2023 requires new or renewing Drug Enforcement Administration (DEA) registrants to complete a total of at least eight hours of accredited continuing education on the treatment and management of patients with opioid or other substance use disorders *before renewal of their license.*

LG Health's CME department offers eight hours of online enduring materials available to satisfy this requirement. The lectures can be found in the CME On Demand "Featured" section at the QR code at right. Additional information about providers excluded from the requirement and what documentation DEA requests is also available.

LG Health's CME department also offers a number of programs on demand addressing a range of topics across different specialties. Recent additions include:

- DVT/PE Prophylaxis State of the Art 2023
- Pediatric Neurology Topics and Headache for the Primary Care Provider
- A Breakthrough for Cdiff

Scan the QR code at right to access the on demand materials, and check the Calendar at the link below for details about the most recent in-person CME offerings.

For details and to register for programs, visit lancastergeneralhealth.org/health-care-professionals/for-physicians/continuing-medical-education.